UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: August 30, 2012
TXR No. 0056440

SUBJECT: **Propoxur**: Review of Acute Comparative Cholinesterase Assay (CCA) Studies, Benchmark Dose Analysis and Derivation of Acute Point of Departure (POD)

PC Code: 047802
Decision No.: 464412
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0056440
MRID No.: 48784801,48784802, 48784803, 48784804

DP Barcode: D401491/ D404194
Registration No.: NA
Regulatory Action: Generic Data Call In
Case No.: NA
CAS No.: NA
40 CFR: NA

FROM: Deborah Smegal, MPH, Toxicologist
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Deborah C Smegal

THROUGH: Felicia Fort, Branch Chief
Registration Action Branch 6 (RAB6)
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Felicia Fort

TO: Kaitlin Keller, Chemical Review Manager (CRM)
Risk Management and Implementation Branch 3
Pesticide Reevaluation Division (PRD) (7508P)

I. CONCLUSIONS

The series of non-guideline cholinesterase (ChE) inhibition studies are acceptable and satisfy the generic data call-in (DCI) requirement for propoxur for a comparative cholinesterase assay (CCA) study in adult rats versus postnatal day (PND) 11 pups.

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OPP's review indicates that the data show lifestage sensitivity (i.e, pups are more sensitive than adults), and that RBC ChE is more than brain AChE inhibition. In recent years, it is typical OPP practice to perform BMD analysis on CCA studies.

OPP performed benchmark dose (BMD) analyses of the CCA on propoxur in order to establish a point of departure (POD) for the single-chemical risk assessment using the agency's Benchmark Dose Software (BMDS). OPP analyzed the registrant-supplied data of red blood cell (RBC) acetylcholinesterase inhibition (AChEI) in male and female PND11 pups (combined sex data) and calculated a BMD10 (Benchmark Dose for 10% inhibition) as 0.0427 mg/kg/day and the BMDL10 (i.e. 95% Lower Bound Confidence Limits on the BMD10) was estimated as 0.0285 mg/kg/day. OPP has concluded that the use of a $BMDL_{10}$ of 0.0285 mg/kg/day will provide a health-protective and scientifically supportable approach for an acute POD.

Based on a comparison of BMD10s, pups were approximately 11 fold more sensitive than the adult rats for brain and RBC cholinesterase inhibition (combined sex data).

II. ACTION REQUESTED

Review the series of non-guideline comparative cholinesterase (ChE) assay studies (MRID 48784801-48784803) that were submitted as required by the registration review Data Call In (DCI).

III. BACKGROUND

A series of non-guideline cholinesterase (ChE) inhibition studies (MRID 48784801-48784803) were undertaken to evaluate any differences between postnatal day 11 (PND 11) pups and adult rats (approximately 7-8 weeks of age) with regard to cholinesterase inhibition for propoxur. These studies are acceptable and satisfy the generic DCI requirement for propoxur for a CCA study in adult rats versus postnatal day (PND) 11 pups. Consistent with the n-methyl carbamates mode of action (MOA), these studies evaluated cholinesterase inhibition following a single dose at the time of peak effect. Both the range finding and definitive studies provide good dose-response data. The definitive study used doses from 0.1 to 1 mg/kg, while the range finding study uses doses from 1 to 10 mg/kg in adults and 0.3 to 3 mg/kg in pups.

IV. RESULTS/DISCUSSION (or MRID Summary Table, etc.)

MRID Summary Table Example

Study Type	MRID	Comments
Non-Guideline Acute Time Course Study	48784801	New DER
Non-Guideline Acute Dose Range Finding Study	48784802	New DER
Non-Guideline Acute Dose-Response Study	48784803	New DER
Non-Guideline Study, Estimation of Benchmark Dose for Propoxur	48784804	Considered in EPA Benchmark Dose Analysis

PROPOXUR/pc CODE 047802 **Non-Guideline**

EPA Reviewer: Deborah Smegal, MPH **Signature:** Deborah C Smegal
Risk Assessment Branch VI, Health Effects Division (7509P) Date 8/30/12
EPA Secondary Reviewer: Elissa Reaves, PhD **Signature:** Mary Elissa R
Risk Assessment Branch IV, Health Effects Division (7509P) Date 9/4/12

TXR#: 0056440

DATA EVALUATION RECORD

STUDY TYPE: Non-guideline; Effects on Brain and RBC Cholinesterase in Adult and Juvenile Rats

PC CODE: 047802 **DP BARCODE:** D401491

TEST MATERIAL (PURITY): Propoxur (98.6% a.i.)

SYNONYMS:

CITATION: Toot, J.D. (2012). A Dose-Response Study of Red Blood Cell and Brain Cholinesterase in Juvenile Rats following Oral (Gavage) Administration of Propoxur WIL Research Laboratories, LLC, Ashland, OH. Laboratory Project ID: WIL-551 010, March 9, 2012. MRID 48784803. Unpublished.

Toot, J.D. (2011). A Time Course Study of the Effects of Propoxur on Red Blood Cell and Brain Cholinesterase in Adult and Juvenile Rats Following Oral (Gavage) Administration. WIL Research Laboratories, LLC, Ashland, OH. Laboratory Project ID: WIL-551008, November 21, 2011. MRID 48784801. Unpublished.

Toot, J.D (2012). A Dose-Range Finding Study of the Effects of Propoxur on Red Blood Cell and Brain Cholinesterase in Adult and Juvenile Rats Following Oral (Gavage) Administration. WIL Research Laboratories, LLC, Ashland, OH. Laboratory Project ID: WIL-551009, March 5, 2012. MRID 48784802. Unpublished.

SPONSOR: Wellmark International, Schaumburg, IL and Bayer HealthCare, Shawnee Mission, KS

EXECUTIVE SUMMARY - This series of non-guideline cholinesterase (ChE) inhibition studies (MRID 48784801-48784803) was undertaken to evaluate any differences between postnatal day 11 (PND 11) pups and adult rats (approximately 7-8 weeks of age) with regard to cholinesterase inhibition.

Time-Course Study (MRID 48784801): The study was divided into 3 phases (Phase I, Phase II and Phase III). Propoxur (98.6% a.i.; Lot #: 1104080407) in corn oil was administered once *via* gavage (5 mL/kg) adult male or PND 11 male pups to determine the time of peak cholinesterase inhibition. Dosing was as follows: (1) Phase I dosing was to 40 adult Crl: CD (SD) rats at a

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dose of 5 mg/kg; (2) Phase II consisted of 12 male PND 11 Crl: CD (SD) rats at a dose of 3 mg/kg to assess signs of overt toxicity and guide dose selection for Phase III; (3) Phase III consisted of 40 male PND 11 Crl: CD (SD) rats at a dose of 3 mg/kg . RBC and brain cholinesterase activities were determined at 15, 30, 60, 120, and 240 minutes after dosing in the adult 5 mg/kg and PND 11 pup 3 mg/kg groups (controls evaluated at 15 or 240 minutes).

Results: All rats (both age groups) survived to scheduled sacrifice. In phase III PND 11 pups, tremors were noted for 12/40 males receiving 3 mg/kg, while no treatment-related clinical findings were noted in adult males in Phase I or PND 11 male pups in Phase II. Maximal RBC (63%) and brain (46%) inhibition was observed at 15 minutes at 5 mg/kg in adult males. In the PND 11 male pup, maximal RBC (74%) and brain (64%) inhibition was observed at 30 minutes at 3 mg/kg. However, RBC and whole brain cholinesterase activity in the 3.0 mg/kg group increased from 0.5- to 4-hours post-dosing (106% and 83%, respectively, at 4 hours), providing evidence of partial recovery in brain. Overall results from the doses evaluated in the time course study suggest that the time of peak inhibition occurred slightly faster in adults (15 minutes) than in PND11 pups (30 minutes), but the PND11 pups took longer to recover. Based on the results of this time-course study, 15 minutes and 30 minutes were selected as the time of peak cholinesterase determination in the definitive dose-response study for adults and PND 11 pups, respectively. Following acute oral exposure to propoxur, brain weights were comparable among the groups in both age groups.

Dose Range-Finding Study (MRID 48784802): This study was performed to determine the dose levels for use in the definitive dose-response study (MRID 48784803). Adult Crl: CD (SD) rats 8 weeks of age (1, 2, 3, 5, or 10 mg/kg) and PND 11 pups (0.3, 0.5, 1, 2, or 3 mg/kg) were administered single doses of propoxur in corn oil 5 ml/kg *via* gavage (6/sex/dose for both age groups). At 15 and 30 minutes post dose for adults and pups, respectively cholinesterase activity was assessed in the RBC and brain compartments.

Results: No test substance-related clinical signs were observed in the adult rats at time of dosing (clinical signs were not recorded in pups due to technician error). A dose-related reduction in ChE activity (both compartments) was observed at all dose levels in both sexes and age groups. In adult rats, mean RBC cholinesterase inhibition (ChEI) ranged from 15% to 84%, while mean whole brain ChEI ranged from 3% to 53%. In PND 11 pups, mean RBC ChEI ranged from 36% to 82%, while mean whole brain ChEI ranged from 22% to 64%. At the common dose of 1.0 mg/kg, RBC cholinesterase was reduced 15-16% in the adult rats compared to 57-58% in the PND 11 pups. Since significant ChE inhibition was observed at the lowest dose in PND11 pups, dosage levels of 0.1, 0.3, and 1.0 mg/kg were selected to further elucidate ChE inhibition at low doses for benchmark analyses in the definitive dose-response study. Brain weights were comparable among the groups in both age groups and sexes.

Dose-Response Study in Pups (MRID48784803): In the definitive dose response study, propoxur (98.6% a.i.; Lot #: 1104080407) was administered once *via* gavage in corn oil (5 ml/kg) to 11 PND 11 pups/sex/dose at dose levels of 0, 0.1, 0.3, or 1.0 mg/kg. Adults were not evaluated since

the range-finding study resulted in adequate inhibition of RBC and brain ChE. RBC and brain ChE were evaluated at the pre-determined time of peak effect of 30 minutes.

Results: *Clinical signs.* There were no treatment-related effects on mortality in either age group. Clinical signs were not recorded for any of the treated pups as per the protocol prior to euthanasia due to technician error. Brain weights were comparable among the male and female PND 11pups.

RBC Cholinesterase Results. As suggested in the dose range-finding study, PND 11 pups were more sensitive than the adult rats based on a comparison of RBC cholinesterase inhibition. In the PND 11 pups, both sexes displayed a dose-related reduction in RBC cholinesterase activity, with females being more sensitive than males. The magnitude of RBC inhibition being 33-49% at 0.3 mg/kg and 64-66% at the highest dose tested (1.0 mg/kg) in both male and female PND11 pups. At 0.1 mg/kg (lowest dose tested), 31% RBC cholinesterase inhibition was observed in the female and 12% in male PND 11 pups.

Brain Cholinesterase. PND 11 pups were more sensitive than the adult rats, based on a comparison of brain ChE inhibition. Brain ChE activity was decreased at all doses in the PND 11 pups (both sexes). The magnitude of the decrease was 7.7 % (M) and 8% (F) at 0.1 mg/kg, 23% (M) and-31% (F) at 0.3 mg/kg, and 55% (M) and 48%(F) at 1.0 mg/kg in the PND11 pups (both sexes).

HED conducted BMD analyses on the propoxur comparative cholinesterase data (CCA) for both adults (MRID 48784802) and PND 11 pups (MRID 48784803) for both RBC and brain compartments. In addition, HED considered the registrant's submitted benchmark dose (BMD) analysis of the cholinesterase findings (Mihlan and Sheets (2012). Estimation of Benchmark Dose for Propoxur Based on RBC Cholinesterase Activity in Post-Natal Day 11 and Adult Rats; MRID 48784804). HED was able to reproduce most of the registrant's BMD analyses for the male and females. In addition, HED evaluated the male and female pup RBC data from the dose response study to see if it was appropriate to combine these data for BMD analysis. Although the statistical tests that show a borderline significant difference in these datasets (p=0.067), HED concluded that these datasets can be combined to provide more robust ChE measures as there is no biological basis to support sex-differences for PND 11 pups, and the observed difference is likely due to variability in the RBC ChE measurements. Details of Agency's BMD analysis are presented in a separate BMD memo (D404194 memo from J. Liccione/ B.Sarkar August 2012 TXR 0056440

These studies are classified as **acceptable/non-guideline**. These studies do not satisfy a guideline requirement for propoxur. They satisfy the generic data call-in requirement for propoxur for a comparative cholinesterase study in adult rats versus postnatal day (PND) 11 pups.

COMPLIANCE - Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

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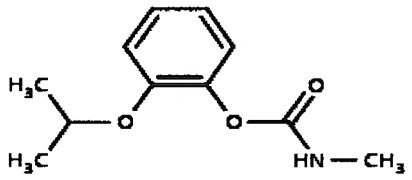
I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Propoxur

Description:	White crystalline powder
Lot #:	1104080407
Purity (w/w):	98.6-98.5% a.i.
Stability:	Expiration date: April 26, 2012; WIL ID # 1100A4
CAS #:	114-26-1
Structure:	



2. Vehicle – corn oil

3. Test animals

Species:	Rat
Strain:	Crl:CD(SD)
Adult age/weight at study initiation:	adult rats 5-6 weeks at receipt; time-mated dams received on GD 10, 11 or 12 (#551008: GD 10; #551009: GD 11 or 12); used to supply PND 11 pups; selected adults ≈7-8 weeks old; body weights:#551008 Phase I 8 week males 244-303g; #551009 7 week males: 206-267g and females: 151-195g.
Pup Age/weight at dosing:	11 days old; males: 18.8-28.6g; #551009 Phase II 20.9-28.9g males and 19-27.2g females; #551108 Phase II males 21-28 g; Phase III males 19-27 g
Source:	Charles River Laboratories, Inc. (Raleigh, NC)
Housing:	Each dam was housed with her litter in a nesting box during the post-natal period. Adults were individually housed in stainless steel, wire bottomed cages.
Diet:	Certified Rodent Diet #5002 (PMI Nutrition International, LLC.), *ad libitum*
Water:	Reverse osmosis treated (on-site) drinking water, *ad libitum*
Environmental conditions:	
Temperature:	22±3°C
Humidity:	50±20%
Air changes:	10/hr
Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	Adults, 16-14 days; pups 0-1 days

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B. STUDY DESIGNS

This series of non-guideline cholinesterase inhibition studies (MRID 48784801-48784803) was undertaken to evaluate any differences between neonatal (postnatal day 11; PND 11) pups and adult rats with regard to cholinesterase (ChE) inhibition as a biomarker for more general neurological effects. Preliminary studies (MRID 48784801; and MRID48784802) were performed to determine the appropriate dose levels for the time to peak effect study and for the definitive dose response study in PND11 pups (MRID48784803) with regard to inhibition of red blood cell (RBC) and brain ChE. The adult ChE data in the range-finding study (n=6/sex/dose) were determined to be adequate by EPA (email from M. Mizens to K. Keller summarizing conclusions of Dose-Response Conference call on 10.25.11), and thus only additional pup data were collected in the definitive dose-response study (MRID 48784803).

2. **In-life dates** - MRID 48784801: WIL 551008: Phase 1 Start: May 10, 2011; End: May 24, 2011; Phase II Start: May 24, 2011; End: June 16, 2011; Phase III Start: June 7, 2011; End: June 30, 2011

   MRID 48784802: WIL 551009: Phase 1 Start: August 16, 2011; End: September 1-2, 2011; Phase II Start: August 30, 2011; End: September 21, 2011

   MRID 48784803: WIL 551010: Start: December 12, 2011 End: December 14, 2011

3. **Animal assignment and treatment** –**Dose Range Finding Study (MRID 48784802). Phase I (adult rats)**: There were 5 propoxur-treated groups and one control group, each consisting of 6 adult rats/sex/group (Table 1). After randomization (based on body weight stratification randomized in a block design), these rats were randomized into 2 study replicates to allow for the reasonable conduct of cholinesterase assessments. Each dose group and sex was ≈equally represented within each study replicate. **Phase II (PND 11 pups):** Pups were randomly assigned to one of 5 treatment groups and one control group; such that no more than 1 pup/sex/litter was assigned to each treatment group; each group consisted of 11 pups/sex/dose. Each dose group and sex was equally represented within each study replicate for dose administration. Adults and pups (on PND 11) received a single gavage dose at a volume of 5 mL/kg body weight.

Study design: Table 1 shows the objectives and treatment groups allocated for the three studies.

TABLE 1. Study Design for Cholinesterase Inhibition Studies on Propoxur

MRID Study #	Dose(s) (mg/kg)	# rats/sex	Objective/Treatment/Termination
48784801 WIL-551008 Toot 2011 Time Course Study	Phase I (adult): 0, 5 Phase II (PND 11 pups): 0, 3 Phase III (PND 11 pups): 0, 3	Phase I (adult 8 weeks of age): 8 males/time point Phase II (PND 11): 12 males treated and 3 control males Phase III (PND 11): 8 males//time point and 17 control males	Determine time to peak inhibition (RBC and brain cholinesterase). Single oral dose in adults (Phase I) and PND 11 (Phase III) male rats. An additional group of PND11 male pups (Phase II) were administered propoxur prior to Phase III to assess for signs of overt toxicity in PND11 pups; Controls: 8 adult (Phase I) and 9 PND 11 pups (Phase III) terminated at 0.25 and 4 hrs, 8 adults (Phase 1) and 8 PND 11 pups (Phase III) terminated at 0.25, 0.5, 1, 2, and 4 hrs post dosing.
48784802 WIL-551009 Toot 2012 Dose Range Finding Study	Phase I (adult): 0, 1, 2, 3, 5, 10 Phase II (PND 11 pups): 0, 0.3, 0.5, 1, 2 and 3	6/sex	Determine dose levels (dose-range finding) for the inhibition of RBC and brain cholinesterase following a single oral dose in adults (Phase I) and PND 11 (Phase II) rats. Single oral dose; clinical observations at approximately 15 and 30 min post-dose for adults and PND 11 pups, respectively; cholinesterase activity (brain and RBC) evaluated within 1 hour post-dose (termination) and sample collection.
48784803 WIL 551010 Toot 2012 Dose-Response Study in Pups	PND 11 pups: 0.1, 0.3, 1	11pups/ sex/dose	Determine the dose-response for inhibition of RBC and brain cholinesterase in PND 11 (Phase II) male and female rats. Single oral dose: PND 11 pups at 30 minutes post dose.

PND = postnatal day

4. <u>Dose selection and sampling time rationale;</u> The dose levels and sampling times selected for the dose-response study in pups (MRID 48784803) were based on the results of the two studies, described below (a, b). Propoxur was administered once *via* gavage (5 ml/kg) to 11 PND 11 pups/sex/dose at dose levels of 0, 0.1, 0.3, 1.0 mg/kg in the definitive dose-response study (MRID 48784803).

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a) Time point selection rationale - A time-course study (MRID48784801; WIL 551008) was conducted in both adults and PND11 male rats in three phases. In Phase 1, 8 adult rats/time point were treated with single (gavage) doses of 0 or 5 mg/kg. In Phases II (12 pups) and III (8 pups/time point), PND11 pups were given a single dose of 3 mg/kg; Phase II pups were assessed for signs of overt toxicity within 12 hours and were discarded, while Phase III pups were evaluated further. For adults (Phase I) and pups (Phase III), RBC and brain cholinesterase activities were analyzed at sacrifice at approximately 15, 30, 60, 120, or 240 minutes post dose (Tables 2 and 3). All animals (both age groups) survived to scheduled sacrifice. In Phase III, tremors were noted in 12/40 males in the 3 mg/kg group. No substance-related clinical signs were noted in adults (Phase I) or the pups in Phase II. In the **adult male rats**, maximal RBC and brain inhibition was present at 15 minutes post dosing (63 and 46%, respectively) to 5 mg/kg. **PND 11 male pups** displayed a maximal RBC and brain inhibition response at 30 minutes at 3 mg/kg (74% and 64%, respectively). Regarding the time to peak effect, time points of 30 minutes and 15 minutes were selected for the PND 11 pups and adult rats, respectively, for the definitive dose-response study (MRID48784803; WIL 551010).

a) Dose selection rationale for time to peak effect study - Dose levels were selected by the Sponsor based on the results of previous studies (Toot,2011, WLL-551008 MRID 48784801 and Toot, 2012, WIL-551009 MRID 48784802). In the time course study (Toot, 2011, WLL-551008), inhibition of RBC and whole brain cholinesterase activity in PND 11 males was observed in the 3.0 mg/kg group, with peak inhibition noted at 0.5 hours following dose administration. However, RBC and whole brain cholinesterase activity in the 3.0 mg/kg group increased (106.0% and 83.0%, respectively) from 0.5- to 4-hours post-dosing, providing evidence of partial recovery. In the dose range-finding study (Toot, 2012, WIL-551009), administration of the test substance at doses of 0.3, 0.5, 1.0, 2.0, and 3.0 mg/kg to PND II pups resulted in a dose-related, statistically significant, reduction in ChE activity in both the brain and RBC compartments at all dose levels in both sexes and age groups (Tables 4 and 5).

The PND 11 pups showed a greater reduction in RBC cholinesterase activity at 1 mg/kg (males/females 57% ChEI) than the adult rats (males 14% ChEI/females 16% ChEI) at the same dose level. Also at 1 mg/kg, PND 11 pups (both sexes) displayed a greater reduction in brain cholinesterase activity (42-47% ChEI) than the adult rats (3-10% ChEI). In pups, RBC inhibition ranged from 36% to 78% in males and from 38% to 82% in females, while whole brain cholinesterase ranged from 22% to 61% in males and from 25% to 64% in females at 0.5 hours following dose administration.

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Table 2. Time Course Study (MRID48784801; WIL 551008) - Mean (±SD) Cholinesterase Activity in **Male PND 11 Pups** Administered Propoxur *via* Gavage (acute)[a]

Time post-dose (minutes)	Dose (mg/kg)	Red Blood Cells		Brain	
		cholinesterase (U/L)	% inhibition	cholinesterase (U/L)	% inhibition
Males					
15	0	6327±920 (adjusted for outlier)	-	24230±1150	-
	3	3288±2595 (a)	48*	14345±5489 (a)	40.8**
30	0	-	-	-	-
	3	1639±279 (a)	74**	8762±1424	63.8**
60	0[c]	--		--	-
	3	2527±1342 (a)	60**	9659±957	60**
120	0	-		-	-
	3	2251±1231 (adjusted) (b)	64**	13820±5098	43*
240	0	4780±993	-	24097±1039.6	-
	3	3375±1246	29.4*	16020±2426	33.8**

a Data were obtained from Table S10 (pages 66-68) of the study report.
n = 8, except where noted; (a) n=7, (b) n=5
* p≤0.05; ** p≤0.01

Table 3. Time Course Study (MRID48784801; WIL551008). Mean (±SD) Cholinesterase Activity in **Male Adult Rats** Administered Propoxur *via* Gavage (acute).

Time post-dose (minutes)	Dose (mg/kg)	Red Blood Cells		Brain	
		Cholinesterase (U/L)	% inhibition	Cholinesterase (U/L)	% inhibition
Males					
15	0	3150±530		49994±1008	
	5	1175±471**	62.7**	27084±5859**	45.8**
30	0	-			
	5	1901±419	40*	30966±2599	38*
60	0	-			
	5	2572±403	18.3*	36666±2459	26.6*
120	0	-			
	5	3093±635	2	43835±1989	12.3
240	0	3482±379		50118±1782	
	5	3467±332	0.4	47978±2392	4.3

a Data were obtained from Table S5 (pages 58-60) of the study report. n = 8; * p≤0.05; ** p≤0.01

Table 4. Study Design and Results (**RBC**) of Range-Finding Study (MRID48784802; WIL 551009)

Dose (mg/kg)	# of rats/sex	RBC Cholinesterase (U/L)		Sample Time (minutes post-dosing)
		Males	Females	
Adults				
0	6	2928±1187.6	3220±894	15
1	6	2499±468↓14.7%	2697±728 ↓16%	15
2	6	2061±792 ↓29.6%	2158±630* ↓33%	15
3	6	1701±934* ↓41.9.7%	1515±645** ↓53%	15
5	6	1453±408* ↓50.4%	1246±427** ↓61%	15
10	6	1120±636** ↓61.7%	485±239** ↓85%	15
PND 11 Pups				
0	6	7657±1187	7158±884	30
0.3	5	4902±683** ↓36%	4444±879** ↓37.9%	30
0.5	5	4459±1062** ↓41.8%	4124±1001** ↓42.4%	30
1	6	3259±573** ↓57.4%	3029±900** ↓57.7%	30
2	4	2470±749** ↓67.7%	1302±294** ↓81.8%	30
3	5	1726±328** ↓77.5%	1547±604** ↓78.4%	30

a Data obtained from Table S9 and S10 (pages 52-53) and Table S15 and S16 (pages 62-63) of the study report.

* $p \leq 0.05$; mean ± s.d.

** $p \leq 0.01$; mean ± s.d.

Table 5. Study Design and Results (**Brain**) of Range-Finding Study (MRID48784802; WIL 551009)

Dose (mg/kg)	# of rats/sex	Brain Cholinesterase (U/L)		Sample Time (minutes post-dosing)
		Males	Females	
Adults				
0	6	52184±1887.5	51558±1322	15
1	6	50600±2619↓3%	46481±2540 ↓9.8%	15
2	6	43686±2300 *↓16.3%	42136±5139 ↓18.3%	15
3	6	41315±3712* ↓20.8%	34790±2268** ↓32%	15

Dose (mg/kg)	# of rats/sex	Brain Cholinesterase (U/L)		Sample Time (minutes post-dosing)
		Males	Females	
5	6	34964±4661** ↓33%	26276±6965** ↓49%	15
10	6	28107±8309** ↓46.1%	24324±13626** ↓52.8%	15
PND 11 Pups				
0	6	23640±1983	24486±812	30
0.3	6	18456±2756** ↓21.9%	18378±2164** ↓24.9%	30
0.5	6	16627±2221** ↓29.7%	15268±2395** ↓37.6%	30
1	6	13719±3004** ↓42%	12856±1936** ↓47.5%	30
2	6	10073±1541** ↓57.4%	10058±3756** ↓58.9%	30
3	6	9149±2023** ↓61.3%	8683±1743** ↓64.5%	30

a Data obtained from Table S9 and S10 (pages 52-53) and Table S15 and S16 (pages 62-63) of the study report.

* $p \leq 0.05$; mean ± s.d.

** $p \leq 0.01$; mean ± s.d.

5. Test substance preparation and analysis –The dose formulations were prepared once as single formulations for each dose level; divided into aliquots for dispensation, and stored refrigerated. The dose formulations were stirred continuously throughout use.

Results:

Homogeneity analysis: The dosing formulations were inspected visually and were found to be visibly homogeneous and acceptable for administration. Homogeneity analyses in MRID 48784803 showed mean % of target to be 91.7%-99.4% for formulations of 0.02, and 0.2 mg/mL. Homogeneity analyses in MRID 48784802 showed mean % of target to be 95.7%-111% for formulations of 0.06, and 0.2 mg/mL.

Stability analysis: In the dose-response study (MRID 48784803), formulations of 0.02, and 0.2 mg/mL were 101%, and 97.1%, respectively, of the mean % of time zero after storage (refrigeration) for 7 days.

Concentration analysis: In the dose-response study (MRID 48784803), the dosing formulations were within the testing laboratories standard operating procedures range for suspensions (85% to 115%) and were within the protocol requirement for concentration acceptability (90% to 110% of target) except for initial 0.02 mg/L formulation that was 157% of target concentration, and was not administered to animals. The 0.02 mg/L dose level was reformulated to be 95.6% of the target concentration. In the range finding study (MRID 48784802) concentration analyses had mean % of target of 97.5%-107% and were within WIL Research Standard Operating Procedure

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(SOP) range for suspensions.

Concentration (% of target): Dose Response Study (PND 11 Pups) (MRID 48784803): 95.6-104%; Dose Range Finding Study (MRID 48784802): Phase I (adults) 97.5- 103%; Phase II (pups): 101-107%.

6. Statistics

Time to peak effect (MRID 48784801) Dose Range Finding Study (MRID 48784802): and dose response (MRID 48784803) studies - All statistical tests were performed using appropriate computing devices or programs. Analyses were conducted using two-tailed tests (except as noted otherwise) for minimum significance levels of 1% and 5%, comparing each test substance-treated group to the control group by sex. Each mean was presented with the standard deviation (S.D.), standard error (S.E.), and the number of animals (N) used to calculate the mean. Due to the use of significant figures and the different rounding conventions inherent in the types of software used, the means, standard deviations, and/or standard errors on the summary and individual tables may differ slightly. RBC and whole-brain cholinesterase data were subjected to a parametric one-way ANOVA (Snedecor and Cochran, 1980) to determine intergroup differences between the control and test substance-treated groups. If the ANOVA revealed significant ($p<0.05$) intergroup variance, Dunnett's test (Dunnett, 1964) was used to compare the test substance-treated groups to the control group. Intergroup comparative statistics were not conducted for body weight and brain weight data.

C. METHODS

1. Observations - Dose-Response Study (MRID 48784803) (Pup data) and Dose Range Finding Study (MRID 48784802) (Adult data)

a. Adults - All adult rats, including dams of offspring, were observed at least twice daily for mortality and moribundity. Clinical examinations were performed prior to dosing, ≈20 minutes following dose administration, and immediately prior to sacrifice (≈5-10 and 20-25 minutes post dose for Phases I and II, respectively).

b. Pups –Pups were sexed on PND 0, 4, 7, and 10. Pretest body weights and detailed physical examinations for each pup were recorded on PND 1, 4, 7, and 10. To reduce variability, litters were culled to 10 pups/litter, 5/sex when possible, on PND 4 using a computerized randomization procedure.

2. Body weight - Body weights of all adult rats and PND 11 pups were recorded initially and used as the basis of randomization into dose groups. Additionally, all rats were weighed on the day of dose administration to determine individual doses.

3. Cholinesterase activity determination – Blood samples and whole brains were collected from each pup at approximately 30 minutes (Dose-Response Study MRID 48784803), and each adult at approximately 15 minutes (Range-Finding Study MRID 48784802) following dose administration for determination of cholinesterase activities as follows. PND 11 pups in the dose response study were anesthetized with isoflurane and euthanized by exsanguination during the

blood collection procedure. In the range finding study, adults and PND11 pups were euthanized by carbon dioxide inhalation. Blood samples (at least 1 mL for adult animals and 0.5 mL for PND 11 pups) were collected from the inferior vena cava into chilled tubes containing sodium heparin as the anticoagulant and centrifuged for ≈ 10 minutes at ≈ 4°C. The plasma was discarded and the packed red blood cells (RBC) were diluted ≈ 1:20 (w:v) using 1% Triton X-100 solution (buffered). The contents of the tube were mixed (vortex mixer) and the RBC preparation was analyzed. Brains were excised from the skull and weighed. Whole brains were diluted ≈ 1:10 (w:v) using 1% Triton X-100 solution (unbuffered) and homogenized. The homogenate was centrifuged for ≈15 minutes at ≈ 4°C, and the supernatant was analyzed. RBC and whole brain cholinesterase activities were determined using an assay based on a modification (Hunter et al., 1997) of the Ellman reaction (Ellman et al., 1961), which uses acetylthiocholine as a substrate to measure total cholinesterase (i.e., the assay is not specific to acetylcholinesterase) *via* a photometric period (WIL SOP No. T5-146-2, dated 9/12/2006). To prevent reactivation of the enzyme, all samples were maintained in an ice-water bath from the point of collection until analysis for cholinesterase activity. The time of each blood sample and brain collection was recorded and samples were analyzed within 1 hour of sample collection, based on the results of a previous validation study of carbamate inhibition of cholinesterase (Roegge, 2009, WIL-99420).

II. RESULTS – Pups: Definitive Dose-Response Study (MRID 48784803) Adults: Dose Range- Finding Study (MRID 48784802)

A. OBSERVATIONS

1. Clinical signs of toxicity

a) Pups – No clinical signs were observed prior to dosing. No clinical observations were recorded post dosing due to technician error, as documented in the protocol deviations.

b) Adults - No clinical signs of toxicity were noted in the adults prior to dosing, or just prior to euthanasia (approximately 5-10 minutes following dose administration) at any dose level.

2. Mortality

a) Pups - All pups survived to scheduled termination.

b) Adults - All adult rats survived until scheduled termination.

B. BODY WEIGHTS - Pups and Adults - Body weights of the treated PND 11 pups and adult rats were comparable to their respective controls on the day of dose administration.

C. CHOLINESTERASE ACTIVITY –The cholinesterase data for both compartments and age groups are summarized and presented below in Tables 6 and 7.

1. Red Blood Cell (RBC) Cholinesterase - Pups. RBC data in pups was evaluated in the definitive dose-response study. RBC cholinesterase activity was decreased (dose-related) in both sexes at 0.5 hour following acute exposure (males decreased 12-66%/females decreased 31-65%) to dose levels ranging from 0.1 to 1.0 mg/kg (Table 7). In males, the mean RBC cholinesterase

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activity in the 0.3 and 1.0 mg/kg groups was statistically significantly ($p<0.01$) lower (33% and 66%, respectively), than the control group. In females, the mean RBC cholinesterase activity in the 0.1, 0.3 and 1.0 mg/kg groups was statistically significantly ($p<0.01$) lower (31%, 49%, and 65% lower, respectively) than the control group.

Adults. Adult ChE data was evaluated in the range-finding study, not the definitive dose-response study. RBC cholinesterase activity was decreased (dose-related) in all dose groups in the adult rats of both sexes at 15 minutes following acute exposure (males decreased 15-62%/females decreased 16-85%) to dose levels ranging from 1.0 to 10 mg/kg (Table 8). With the sexes combined, the reductions were 15-74%. At lower doses, males and females had similar responses (1 and 2 mg/kg), but at higher doses females had a greater response than males (i.e., 42% vs. 53% at 3 mg/kg, 50% vs. 61% at 5 mg/kg and 62 vs. 85% at 10 mg/kg for males and females, respectively). At the common dose of 1.0 mg/kg, RBC cholinesterase was reduced 15-16% in the adult rats compared to 65% in the PND 11 pups.

2. Brain Cholinesterase- Pups- Brain cholinesterase activity was decreased at all doses compared to the control values in the male (8-55%) and female (8-48%) PND 11 pups (Table 7). A BMD analysis will provide a level at which 10% inhibition was observed. In males, mean whole brain activity was statistically significantly ($p<0.01$ or $p<0.05$) lower in all three dose groups relative to the control group. In females, whole brain cholinesterase activity was statistically significantly ($p<0.01$) lower than the control in the 0.3 and 1 mg/kg/day groups.

Adults – Brain cholinesterase activity was decreased at all doses in male (16-46%) and female (10-53%) adult rats except the lowest dose in the male rats (Table 8). At the common dose of 1.0 mg/kg, brain cholinesterase was reduced 3-10% in the adult rats compared to 48-55% in the PND 11 pups.

Table 6. PND 11 pup cholinesterase results from definitive dose-response study (MRID 48784803)

Sex	0 mg/kg	0.1 mg/kg	0.3 mg/kg	1.0 mg/kg
RBC Cholinesterase (U/L)				
PND 11 Males %↓	6737±1121.1	5916±986.3 12.2	4532±1319.4 32.7**	2323±591.8 65.5**
range	5416-8782	4796-7918	2182-6364	1474-3396
PND 11 Females %↓	6994±2057.7	4856±489.9 30.6**	3544±1166 49.3**	2460±900.1 64.8**
range	4188-10758	4244-5530	2196--6124	1474-3848
Brain Cholinesterase (U/L)				
PND 11 Males %↓	23708±1480.1	21887±1315.5 7.7*	18250±1639.2 23**	10594±1190 55.3**
range	21082-26230	19796-24692	14277-19866	9040-12595
PND 11 Females %↓	24263±1220.8	22320±1610.7 8	16844±2432,9 30.6**	12592±2300 48.1**
range	22959-27078	19117-24191	14305-21859	9641-17993

Data obtained from Table S7 and S8 (pages 42-43) and Table A7/A8 (pages 187--194) of the study report; * Dunnett's p-value # <0.05 or **p<0.01; ◀Dunnett's test was used to make pairwise comparisons of each individual treated group with the control group.

Table 7. Adult cholinesterase results from the range-finding study (MRID 48784802)

Sex	0 mg/kg	1 mg/kg	2 mg/kg	3 mg/kg	5 mg/kg	10 mg/kg
RBC Cholinesterase (U/L)						
Males %↓	2928±1187.6	2499±468.4 15	2061±792 .5 30	1701±934.8 42*	1453±408.5 50*	1120±636.4 62**
Range	1892-5020	1920-3196	1058-3168	520-2928	874-1980	794-2362
Females %↓	3220±894.9	2697±728.8 16	2158±630.1 33*	1515±645.9 53**	1246±427.5 61**	485±239.5 85**
Range	1962-4270	1652-3532	1270-3220	606-2278	818-1764	252-902
Brain Cholinesterase (U/L)						
Males %↓	52184±1887.5	50600±2619.9 3	43686±2300.2 16*	41315±3712.8 21**	34964±4661 33**	28107±8309.1 46**
Range	50068-54796	47460-54647	41150-46719	34861-43627	30790-40971	19611-39910
Females %↓	51558±1322.9	46481±2540.1 10	42136±5139.1 18	34790±2268.7 33**	26276±6965 49**	24324±13626 53**
Range	49750-53396	42747-49686	36182-48124	32210-38267	17979-37048	16975-52060

Data obtained from Table 4 (pages 48-49) and Tables A9/A10 (pages 215-270) of the study report; n = 6 rat/sex/group
*statistically significant * Dunnett's p-value *p<0.05, or ** p<0.01

D. BRAIN WEIGHT - Following acute oral exposure to propoxur, brain weights were comparable among the groups in both age groups and sexes in all three studies (time course, dose response and dose range finding).

E. BENCHMARK DOSE (BMD) ANALYSIS: HED conducted BMD analyses on the propoxur comparative cholinesterase data (CCA) for both adults (MRID 48784803) and PND 11 pups (MRID 48784802) for both RBC and brain compartments. The results are presented in Table 8. In addition, HED considered the registrant's submitted benchmark dose (BMD) analysis of the cholinesterase findings (Mihlan and Sheets (2012). Estimation of Benchmark Dose for Propoxur Based on RBC Cholinesterase Activity in Post-Natal Day 11 and Adult Rats; MRID 48784804). HED has reviewed the submission to verify the BMD analysis of the cholinesterase data presented in MRID 48784804. HED conducted a confirmatory analysis using EPA's Benchmark Dose Software (BMDS) 2.1.1, the same software used in MRID 48784804 and was able to reproduce the registrant's BMD analyses for the male and females.

In addition, HED evaluated the male and female pup RBC data from the dose response study to see if it was appropriate to combine these data for BMD analysis. The registrant proposed that the Agency use the combined BMDL10 for regulatory purposes. To evaluate the merit of this approach, HED conducted a Likelihood ratio test (LRT) for RBC pup data based on the BMD output. The result of the LRT is not statistically significant because p value is greater than conventional alpha level of 0.05. Thus the likelihood-based evaluation suggests that the male and female PND11 RBC data can be combined in the dose-response modeling. EPA also believes that there is no biological basis for gender-based differences in AChE inhibition in

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PND11 rats with N-methyl carbamates, like propoxur. Given the lack of statistical significance, and lack of biological basis for gender based difference in RBC at PND11 HED has concluded that male and female data for PND11 pups can be combined for deriving more robust POD for AChE inhibition at this age.

Details of Agency's BMD analysis are presented in a separate BMD memo (D404194 memo from J. Liccione/ B.Sarkar August 30, 2012 TXR 0056440).

Table 8
Summary of OPPs Benchmark Dose (BMD) Analyses for RBC and Brain ChE inhibition

Sex	Target Organ	Adult[A] (MRID 48784802 Range Finding Study)		PND 11 Pups[A] (MRID 48784803 Dose Response Study)		PND 11 Pups[A] (MRID 48784802 Range Finding Study)	
		BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$
Male	Brain	1.26	1.09	0.13	0.12	0.14	0.11
	RBC	0.73	0.498	0.094	0.075	0.1	0.08
Female	Brain	0.88	0.76	0.08	0.06	0.1	0.08
	RBC	0.55	0.46	0.02	0.01	0.088	0.067
Combined Sexes	Brain	1.29	1.04	0.122	0.0875	---	---
	RBC	0.474	0.339	0.0427	0.0285	---	---

A Adult BMDs based on data in MRID 48784802; PND11 pup BMDs based on data in MRID 48784802, and MRID 48784803.

III. DISCUSSION and CONCLUSIONS

A.INVESTIGATORS' CONCLUSIONS (from Report Summary) - Based on the time to peak effect study (MRID 48784801) in adult rats and PND 11 pups, the investigators concluded that 15 minutes post-dosing was the appropriate time to sample blood and brain tissue for cholinesterase activity in the adult phase and 30 minutes post-dosing was appropriate in the PND 11 pup phase of the comparative dose-response study. Recovery of ChE activity was observed at 4 hours post dosing for adults administered 5 mg/kg, while complete recovery time was not identified for pups given 3 mg/kg.

In the range finding study (MRID 48784802) a dose-related reduction in cholinesterase activity (both compartments) was observed at all dose levels in both sexes of adults and PND 11 pups (adults: 1, 2, 3, 5, or 10 mg/kg and PND 11 pups: 0.3, 0.5, 1, 2, or 3 mg/kg). In adult rats, mean RBC cholinesterase inhibition (ChEI) ranged from 15% to 85%, while mean whole brain ChEI ranged from 3% to 53%. In pups, the lowest dose tested of 0.3 mg/kg resulted in 36-38% RBC ChE inhibition and 22-28% brain ChEI (both statistically significant).

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In the dose response study (MRID 48784803) with PND 11 pups, both sexes displayed a dose-related reduction in RBC cholinesterase activity at ≥ 0.3 mg/kg for males and ≥ 0.1 mg/kg for females. The inhibition of brain ChE activity was observed at ≥ 0.3 mg/kg for males and females. In PND 11 males, mean RBC ChEI ranged from 33 to 66% and brain ChEI ranged from 23-55%. In PND 11 females, mean RBC inhibition ranged from 31% to 65% and brain ChEI ranged from 31% to 48%.

The investigators did not identify a no-observed-effect level (NOEL) for adults or pups, although at 2 mg/kg statistically significant RBC ChEI (33%) was noted in adult female rats, and statistically significant brain ChEI (16%) was noted in adult male rats. In pups, the lowest dose tested of 0.1 mg/kg in the definitive dose response study resulted in 31% and 12% RBC ChE inhibition in female pups (statistically significant) and male pups (not significant), respectively.

B. REVIEWER COMMENTS - There were no treatment-related effects on mortality following acute oral exposure to propoxur in either adult rats or PND11 pups. The time to peak effect is 15 minutes post-dosing for adults and 30 minutes for PND 11 pups following propoxur doses of 5 mg/kg and 3 mg/kg, respectively. In the time course study, tremors were noted for 12/40 PND 11 pups given 3 mg/kg propoxur between 0.25 and 1 hour post-dosing, while no treatment-related clinical findings were noted in adult males dosed with 5 mg/kg propoxur. PND 11 male pups with tremors displayed corresponding RBC and brain inhibition of 48-74% and 41-64%, respectively between 15 and 60 minutes post-dosing with 3 mg/kg. In adult males, RBC and whole-brain cholinesterase levels were similar to those in the control group at approximately 4-hours post-dosing, indicating complete recovery. For PND11 male pups, RBC and whole brain cholinesterase activity in the 3.0 mg/kg pup group increased from 0.5- to 4-hours post-dosing (l06% and 83%, respectively, at 4 hours), providing evidence of partial recovery in brain of pups. Overall results from the doses evaluated in the time course study suggest that the time of peak inhibition occurred slightly faster in adults (15 minutes) than in PND11 pups (30 minutes), but the PND11 pups took longer to recover.

In the range finding study (MRID 48784802) there was a greater amount of inhibition in pups at a similar dose in adults and there was significant inhibition at a much lower dose than adults. Both sexes of PND 11 pups displayed significant brain cholinesterase inhibition (22% -64%) at dose levels of 0.3 mg/kg – 3 mg/kg for both sexes, whereas a similar but lower level of brain inhibition (3%-53%) occurred in both sexes of the adult rats at 1 mg/kg to 10 mg/kg. Significant RBC cholinesterase inhibition (>36%) was observed in the PND 11 pups at 0.3 mg/kg and above, whereas the adult rat displayed this level of RBC cholinesterase inhibition at 2 mg/kg and above. At the common dose of 1.0 mg/kg, RBC cholinesterase was reduced 15-16% in the adult rats compared to 57-58% in both sexes of PND 11 pups.

In the dose response study (MRID 48784803) with only PND 11 pups, both sexes displayed a dose-related reduction in RBC cholinesterase activity, with females being more sensitive than males. The magnitude of inhibition was 33% for males and 49% for females at 0.3 mg/kg and approximately 65% (both sexes) at the highest dose tested (1.0 mg/kg). At 0.1 mg/kg (lowest dose tested), 31% and 12% RBC cholinesterase inhibition was observed in the female and male PND 11 pups, respectively, which was statistically significant for female pups. In PND pups, brain cholinesterase activity was decreased at all doses in both sexes. The magnitude of the

decrease was 7.7-8% at 0.1 mg/kg, 23-31% at 0.3 mg/kg, and 48-55% at 1.0 mg/kg in the PND11 pups (both sexes).

The studies are classified as **acceptable/non-guideline.** These studies do not satisfy a guideline requirement for propoxur. They satisfy the generic data call-in requirement for propoxur for a comparative cholinesterase study in adult versus postnatal day (PND) 11 pups.

D. STUDY DEFICIENCIES – None that would impact study interpretation. The description of the cholinesterase assay procedures lacks sufficient details.

APPENDIX A - SUMMARY TABLES

Summary Table 1. PND11 Rat Control Values Across Studies	
Males PND11 RBC U/L	
MRID 48784802[A] range finding study	7657±1187
MRID 48784801 (time-course) 15 minutes 240 minutes	 6327±920 4780±993
MRID 48784803[A] (dose-response)	6737±1121.1
Females PND11 RBC U/L	
MRID 48784802[A]	7158±884
MRID 48784801	Not tested
MRID 48784803[A]	6994±2057.7
Males PND11 Brain U/L	
MRID 48784802[A]	23940±1983
MRID 48784801 15 minutes 240 minutes	 24230±1150 24097±1039.6
MRID 48784803[A]	23708±1480.1
Females PND11 Brain U/L	
MRID 48784802[A]	24486±812
MRID 48784801	Not tested
MRID 48784803[A]	24263±1220.8

[A] 30 minutes post dose

Summary Table 2. Adult Rat Control Values Across Studies	
Males- Adult RBC U/L	
MRID 48784802[A]	2928±1187.6
MRID 48784801 15 minutes 240 minutes	 3150±530 3482±379
MRID 48784803[A]	2928±1187.6
Females- Adult RBC U/L	
MRID 48784802[A]	3220±894
MRID 48784801	Not tested
MRID 48784803 [A]	3220±894.9
Males –Adult Brain U/L	
MRID 48784802[A]	52184±1887.5
MRID 48784801 15 minutes 240 minutes	 49994±1008 50118±1782
MRID 48784803 [A]	52184±1887.5
Females –Adult Brain U/L	
MRID 48784802[A]	51558±1322
MRID 48784801	Not tested
MRID 48784803 [A]	51558±1322.9

[A] 15 minutes post dose; NT females not tested

Summary Table 3. PND 11 Pup Cholinesterase Values Across Studies at 2 Common Dose Levels			
PND 11 Pup RBC Cholinesterase Values U/L			
Study	**Control**	**0.3 mg/kg**	**1.0 mg/kg**
Males			
MRID 48784802[A] range finding study	7657 ± 1187	4902±683 (↓36%)**	3259±573 (↓57.4%)**
MRID 48784803[A] (dose-response)	6737 ± 1121.1	4532±1319.4 (↓32.7%)**	2323±591.8 (↓65.5%)** -
Females			
MRID 48784802[A] range finding study	7158±884	4444±879 (37.9%)**	3029±900 (↓57.7%)**
MRID 48784803[A] (dose-response)	6994±2057.7	3544±1166 (49.3%)**	2460±900.1 (↓64.8%)** -
PND 11 Pup Brain Cholinesterase Values U/L			
Males			
MRID 48784802[A] range finding study	23640±1983	18456±2756 (21.9%)	13719±3004 (↓42%)**
MRID 48784803[A] (dose-response)	23708±1480.1	18250±1639.2 (23%)**	10594±1190 (↓55.3%)**
Females			
MRID 48784802[A] range finding study	24486±812	18378±2164 (↓24.9%)**	12856±1936 (↓47.5%)**
MRID 48784803[A] (dose-response)	24263±1220.8	16844±2432.9 (↓30.6%)**	12592±2300 (↓48%)**

(↓% inhibition at 30 minutes; * $p<0.05$; ** $p<0.01$; mean± s.d.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: August 30, 2012

SUBJECT: Propoxur: Benchmark Dose Analysis of Acute Oral Studies and Derivation of a Point of Departure.

PC Code: 047802
Decision No.: 464412
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0056440
MRID No.: NA

DP Barcode: D404194
Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: NA
40 CFR: NA

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I. CONCLUSIONS

OPP performed benchmark dose (BMD) analyses of the comparative cholinesterase assay (CCA) on propoxur in order to establish a point of departure (POD) for the single-chemical risk assessment using the agency's Benchmark Dose Software (BMDS). OPP analyzed the registrant-supplied data of red blood cell (RBC) acetylcholinesterase inhibition (AChEI) in male and female PND11 pups (combined sex data) and calculated a BMD10 (Benchmark Dose for 10% inhibition) as 0.0427 mg/kg/day and the BMDL10 (i.e. 95% Lower Bound Confidence Limits on the BMD10) was estimated as 0.0285 mg/kg/day. OPP has concluded that the use of a $BMDL_{10}$ of 0.0285 mg/kg/day will provide a health-protective and scientifically supportable approach for an acute POD.

Based on a comparison of BMD10s, pups were approximately 11 fold more sensitive than the adult rats for brain and RBC cholinesterase inhibition (combined sex data). However, male pups were between 7 and 10 fold more sensitive than male adults, while female pups were between 6 and 28 fold more sensitive than female adults for brain and RBC cholinesterase inhibition.

This memo summarizes the approach and presents the results of BMD analyses and POD derivation.

II. BACKGROUND

A series of non-guideline cholinesterase (ChE) inhibition studies (MRID 48784801-48784803) were undertaken to evaluate any differences between postnatal day 11 (PND 11) pups and adult rats (approximately 7-8 weeks of age) with regard to cholinesterase inhibition for propoxur. These CCA studies consist of a Time-Course Study (MRID 48784801), a Dose Range-Finding Study in both adults and pups (MRID 48784802) and a Dose-Response Study in Pups (MRID48784803). Consistent with the n-methyl carbamates mode of action (MOA), these studies evaluated cholinesterase inhibition following a single dose at the time of peak effect. These studies are classified as acceptable/non-guideline and satisfy the generic data call-in requirement for propoxur for a comparative cholinesterase study in adult rats versus postnatal day (PND) 11 pups. Both the range finding and definitive studies provide good dose-response data. The definitive study used doses from 0.1 to 1 mg/kg, while the range finding study uses doses from 1 to 10 mg/kg in adults and 0.3 to 3 mg/kg in pups.

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OPP's review indicates that the data show lifestage sensitivity (i.e, pups are more sensitive than adults), and that RBC ChE is more than brain AChE inhibition. In recent years, it is typical OPP practice to perform BMD analysis on CCA studies.

The Registrant conducted an analysis and submitted in findings (Mihlan and Sheets (2012). Estimation of Benchmark Dose for Propoxur Based on RBC Cholinesterase Activity in Post-Natal Day 11 and Adult Rats; MRID 48784804). OPP has conducted an independent analysis. Both are discussed in this memo.

III. METHODS

OPP's BMD analyses were performed with EPA's Benchmark Dose Software (Version 2.1.1). The data selected for evaluation consisted of brain and red blood cell (RBC) acetylcholinesterase (AChE) activities from PND11 and adult rat OPP has previously used the exponential model for modeling ChE activity, except when the data fit another model better. In the case of the propoxur CCA study, OPP has used an exponential model, except for female and combined PND11 pups where the Hill model provided a better fit of the RBC cholinesterase data. Model runs for ChE activity were conducted with the benchmark response level of 10% , and statistical (e.g., goodness of fit values, AIC criteria, scaled residual, etc.) and graphical results were used in model evaluation (USEPA 2000, 2002).

The registrant proposed that the Agency use the combined BMDL10 for regulatory purposes. To evaluate the merit of this approach, HED conducted a Likelihood ratio test (LRT) for RBC pup data based on the BMD output. This analysis is provided in Appendix A. The result of the LRT is not statistically significant because p value is greater than conventional alpha level of 0.05. Thus the likelihood-based evaluation suggests that the male and female PND11 RBC data can be combined in the dose-response modeling. EPA also believes that there is no biological basis for gender-based differences in AChE inhibition in PND11 rats with N-methyl carbamates, like propoxur. Given the lack of statistical significance, and lack of biological basis for gender based difference in RBC at PND11 HED has concluded that male and female data for PND11 pups can be combined for deriving more robust POD for AChE inhibition at this age.

IV. Comparison to Registrant BMD analysis

The registrant used a slightly different version of BMD (although there is no important difference between the versions), and only conducted BMDs for RBC ChE. In addition, the registrant utilized a heterogeneous variance model for both male and female RBC datasets; however, HED applied a homogeneous variance model to the male RBC dataset since it provided a better fit. Also, for adult RBC ChE, the registrant dropped the high dose in their analyses for both males and females. HED only dropped the high dose for the males because HED could not obtain an adequate fit for male data. However, the female adult data analyses resulted in an adequate fit (without dropping the high dose group). It is HED policy to utilize the entire dose

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response whenever possible. The HED BMD10 and BMDL10 results for adult male RBC ChE are comparable to the registrant's results, while the BMD10 and BMDL10 results for adult female RBC ChE were slightly higher than the registrant's estimates (likely because HED did not drop the high dose group in the analysis).

For male and female pup RBC ChE, HED obtained comparable results as the registrant (BMDL10 approximately = 0.08 mg/kg for males and 0.01 mg/kg for females). HED agrees with the registrant that the Hill model is the best fit for the female and combined pup RBC ChE data. In addition, HED calculated BMDs using the exponential model for comparison purposes, although the Hill model provides a better fit of the data (as shown in Table 2).

The registrant also included Likelihood Ratio Test (LRT) to evaluate the appropriateness of combining sexes statistically. HED reviewed the analysis of LRT test and was able to replicate the result (i.e. p value) of LRT test for PND11 RBC. See Appendix A.

V. RESULTS

The results of the BMD analyses are summarized in Table 1 below. Details are included in Appendix A. HED was able to reproduce most of the registrant's BMD analyses for the male and females (Mihlan and Sheets 2012). In addition, HED evaluated the male and female pup RBC data from the dose response study to see if it was appropriate to combine these data for BMD analysis.

HED concluded that these datasets can be combined to provide more robust ChE measures as there is no biological basis to support sex-differences for PND 11 pups. In addition, the statistical test also did not find significant difference in these datasets (p=0.067) at conventional alpha level 0.05.

HED also conducted BMD analysis of the PND11 pup data from the range finding study that used a smaller sample size (n=6 sex/dose) for comparison with the BMD estimates from the dose response study (n= 11/sex/dose) and these BMDs are shown in Table 1.

Details of Agency's BMD analysis are presented in Appendix B.

Table 1
Summary of OPPs Benchmark Dose (BMD) Analyses for RBC and Brain ChE inhibition

Sex	Target Organ	Adult[A] (MRID 48784802 Range Finding Study)		PND 11 Pups[A] (MRID 48784803 Dose Response Study)		PND 11 Pups[A] (MRID 48784802 Range Finding Study)	
		BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$
Male	Brain	1.26	1.09	0.13	0.12	0.14	0.11
	RBC	0.73	0.498	0.094	0.075	0.1	0.08
Female	Brain	0.88	0.76	0.08	0.06	0.1	0.08
	RBC	0.55	0.46	0.02	0.01	0.088	0.067
Combined Sexes	Brain	1.29	1.04	0.122	0.0875	---	---
	RBC	0.474	0.339	0.0427	0.0285	---	---

A Adult BMDs based on data in MRID 48784802; PND11 pup BMDs based on data in MRID 48784802, and MRID 48784803.

Table 2
Summary Statistics of PND 11 Pup Cholinesterase Data as Reported by the Registrant (MRID 48784803) (a)

sex	age	Time post dosing	Time unit	dose	Mean ChE Activity	ChE unit	sd	n
Acute RBC								
Males	PND11	0.5	hr	0	6737	U/L	1121.1	9
	PND11	0.5	hr	0.1	5916	U/L	986.3	9
	PND11	0.5	hr	0.3	4532	U/L	1319.4	9
	PND11	0.5	hr	1	2323	U/L	591.8	8
Females	PND11	0.5	hr	0	6994	U/L	2057.7	9
	PND11	0.5	hr	0.1	4856	U/L	489.9	8
	PND11	0.5	hr	0.3	3544	U/L	1166	10
	PND11	0.5	hr	1	2460	U/L	900.1	10
M + F	PND11	0.5	hr	0	6865.67	U/L	1612.92	18
	PND11	0.5	hr	0.1	5416.94	U/L	942.63	17
	PND11	0.5	hr	0.3	4012.21	U/L	1307.87	19
	PND11	0.5	hr	1	2398.9	U/L	760.28	18
Acute Brain								
Males	PND11	0.5	hr	0	23708	U/L	1480.1	11
	PND11	0.5	hr	0.1	21887	U/L	1315.5	11

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sex	age	Time post dosing	Time unit	dose	Mean ChE Activity	ChE unit	sd	n
	PND11	0.5	hr	0.3	18250	U/L	1639.2	11
	PND11	0.5	hr	1	10594	U/L	1190	11
	PND11	0.5	hr	0	24263	U/L	1220.8	11
	PND11	0.5	hr	0.1	22320	U/L	1610.7	11
Females	PND11	0.5	hr	0.3	16844	U/L	2432.9	11
	PND11	0.5	hr	1	12592	U/L	2300	11
	PND11	0.5	hr	0	23985.82	U/L	1354.13	22
	PND11	0.5	hr	0.1	22103.86	U/L	1452.14	22
	PND11	0.5	hr	0.3	17547.18	U/L	2148.51	22
M + F	PND11	0.5	hr	1	11593.18	U/L	2058.85	22

(a) Combined male and female statistics calculated by EPA.

Table 3
Summary Statistics of Acute Adult Cholinesterase Data in Range Finding Study (MRID 48784802)

Sex	Time post dosing	Time unit	Dose mg/kg	ChE Activity	ChE unit	sd	n
Acute RBC							
M	0.25	hr	0	2928	U/L	1187.6	6
M	0.25	hr	1	2499	U/L	468.4	6
M	0.25	hr	2	2061	U/L	792 .5	6
M	0.25	hr	3	1701	U/L	934.8	6
M	0.25	hr	5	1453	U/L	408.5	6
M	0.25	hr	10	1120	U/L	636.4	6
F	0.25	hr	0	3220	U/L	894.9	6
F	0.25	hr	1	2697	U/L	728.8	6
F	0.25	hr	2	2158	U/L	630.1	6
F	0.25	hr	3	1515	U/L	645.9	6
F	0.25	hr	5	1246	U/L	427.5	6
F	0.25	hr	10	485	U/L	239.5	6
M + F	0.25	hr	0	3074	U/L	1014	12
M + F	0.25	hr	1	2598	U/L	593	12
M + F	0.25	hr	2	2109.5	U/L	684	12
M + F	0.25	hr	3	1607	U/L	772	12
M + F	0.25	hr	5	1349	U/L	413	12

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Sex	Time post dosing	Time unit	Dose mg/kg	ChE Activity	ChE unit	sd	n
M + F	0.25	hr	10	802.8	U/L	565.8	12
Acute Brain							
M	0.25	hr	0	52184	U/L	1887.5	6
M	0.25	hr	1	50600	U/L	2619.9	6
M	0.25	hr	2	43686	U/L	2300.2	6
M	0.25	hr	3	41315	U/L	3712.8	6
M	0.25	hr	5	34964	U/L	4661. 7	6
M	0.25	hr	10	28107	U/L	8309.1	6
F	0.25	hr	0	51558	U/L	1322.9	6
F	0.25	hr	1	46481	U/L	2540.1	6
F	0.25	hr	2	42136	U/L	5139.1	6
F	0.25	hr	3	34790	U/L	2268.7	6
F	0.25	hr	5	26276	U/L	6965.7	6
F	0.25	hr	10	24324	U/L	13626.8	6
M + F	0.25	hr	0	51870	U/L	1587.9	12
M + F	0.25	hr	1	48540	U/L	3268	12
M + F	0.25	hr	2	42911	U/L	3881	12
M + F	0.25	hr	3	37755	U/L	4438	12
M + F	0.25	hr	5	30620	U/L	7247	12
M + F	0.25	hr	10	26215	U/L	10940	12

VI. Recommendation for POD for Single Chemical Risk Assessment.

Based on the analyses, it is concluded that the use of a $BMDL_{10}$ of 0.0285 mg/kg/day for red blood cell (RBC) cholinesterase inhibition (ChEI) in male and female PND11 pups (combined sex data) will provide a health-protective and scientifically supportable approach for an acute POD.

VII. References

U.S. EPA 2000. Benchmark Dose Guidance Document. October 2000.

U.S EPA 2002. "Organophosphate pesticides: revised cumulative risk assessment." June 2002.

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Appendix A.

LRT calculation for PND11 RBC ChE data: It should be noted that the best fitted model in terms of AIC, scaled residual and visual inspection for PND11 male RBC is Exponential model (2); on the other hand , the best fitted model for female PND11 RBC and combined PND11 RBC data set is Hill model (lowest AIC value).

However, a common model is needed that provides at least a marginal fit to all three datasets (male, female and combined sexes) to conduct a likelihood ratio test (LRT). The Exponential model 4 meets this criterion.

The Likelihood Ratio test can be conducted using the following asymptotic result:
Chi-Square("Number of Parameters") = -2 × {Logarithm Likelihood Model Fit to Combined Males & Females - (Logarithm Likelihood Model Fit to Males + Logarithm Likelihood Model Fit to Females)};

Where

"Number of Parameters" is the degrees of freedom and is equal to the number of parameters in the model. The distribution of test statistic follows a Chi-Square distribution with "Number of Parameters" degrees of freedom.

The Log- Likelihood value for PND11 male for exponential model(4) with heterogeneous variance = -257.6347-32.16 = -289.7947

The Log- Likelihood value for PND11 female for exponential model(4) with heterogeneous variance= -278.8974-34 =-312.8974

The Log-Likelihood for PND11 combined dataset for exponential model (4) with heterogeneous variance= -541.693-66.16= -607.853

The chi-square test statistic = -2*(-607.853-(-289.7947-312.8974))=-2*(-5.1609)=10.3218
DF=5
p value= 0.067.
Note registrant also derived the same p value.

The result of the LRT is not statistically significant at conventional alpha=0.05 level. Thus the likelihood-based evaluation suggests that the male and female PND11 RBC data can be combined in the dose-response modeling

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APPENDIX B
(EPA Analyses)

Table B-1
Results of EPA BMD Modeling for Brain & RBC ChE in PND11
Males and Females Treated with Propoxur

Sex	Compartment	BMD Results[a] (mg/kg/day)	
		BMD_{10}	$BMDL_{10}$
Dose Response Study (48784802) (n=11 sex/dose) (b)			
Male	Brain	0.13 Exponential 2	0.12 Exponential 2
Female	Brain	0.08 Exponential 4	0.06 Exponential 4
Combined Male and Female	Brain	0.122 Exponential 5	0.0875 Exponential 5
Male	RBC	0.094 Exponential 2	0.075 Exponential 2
Female	RBC	0.021 Hill Model (Best Fit of data) 0.032 Exponential 2	0.010 Hill model (Best Fit of data) 0.019 Exponential 2
Combined Male and Female	RBC	0.0427 Hill Model	0.0285 Hill Model
Range Finding Study (48784802) (n=4-6 sex/dose)			
Male	Brain	0.145	0.1095
Female	Brain	0.1	0.082
Male	RBC	0.1	0.080
Female	RBC	0.088	0.067

[a]Exponential Model with BMR = 10%, unless noted. EPA BMDS Software
(b) source: MRID 48784803

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Table B-2
Results of EPA BMD Modeling for Brain & RBC ChE in ADULT Males and Females Treated with Propoxur[a]

Sex	Compartment	BMD Results[a] (mg/kg/day)	
		BMD_{10}	$BMDL_{10}$
Male	Brain	1.26[b] Exponential 2	1.09[b] Exponential 2
Female		0.88 Exponential 2	0.76 Exponential 2
Combined Male and Female		1.29 Exponential 5	1.04 Exponential 5
Male	RBC	0.7309[b] Exponential 2	0.4982[b] Exponential 2
Female		0.55 Exponential 2	0.46 Exponential 2
Combined Male and Female		0.474 Exponential 4	0.339 Exponential 4

Source: MRID 48784802
[a]Exponential Model with BMR = 10%. EPA BMDS Software
[b]High dose dropped.

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PND 11 Female Pup BMD Analyses for RBC ChE Inhibition Using Hill Model

PROPOXUR - PND11 Female RBC
BMDS 2.1.2 – Hill Model (model variance)
BMR = 10%

Data set: MRID 48784803 acute RBC Females PND11

time		dose	ChE		SD	
0.5	hr	0	6994	U/L	2057.7	9
0.5	hr	0.1	4856	U/L	489.9	8
0.5	hr	0.3	3544	U/L	1166	10
0.5	hr	1	2460	U/L	900.1	10

```
================================================================================
        Hill Model. (Version: 2.15;  Date: 10/28/2009)
        Input Data File: C:/Usepa/BMDS212/Data/hil_Testrunscontinuous_Opt.(d)
        Gnuplot Plotting File:  C:/Usepa/BMDS212/Data/hil_Testrunscontinuous_Opt.plt
                                                Mon Jun 18 11:24:15 2012
================================================================================

BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function is:

  Y[dose] = intercept + v*dose^n/(k^n + dose^n)


  Dependent variable = Mean
  Independent variable = Dose
  Power parameter restricted to be greater than 1
  The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

  Total number of dose groups = 4
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                        lalpha =      14.3278
                           rho =            0
                     intercept =         6994
                             v =        -4534
                             n =      0.94713
                             k =     0.119665


          Asymptotic Correlation Matrix of Parameter Estimates
```


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(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-1	0.1	-0.23	0.086
rho	-1	1	-0.11	0.23	-0.086
intercept	0.1	-0.11	1	-0.71	-0.51
v	-0.23	0.23	-0.71	1	-0.16
k	0.086	-0.086	-0.51	-0.16	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	2.76865	4.68109	-6.40613	11.9434
rho	1.35729	0.562229	0.255342	2.45924
intercept	7056.86	534.476	6009.3	8104.41
v	-5125.22	640.528	-6380.63	-3869.81
n	1	NA		
k	0.128476	0.0582209	0.0143652	0.242587

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	9	6.99e+003	7.06e+003	2.06e+003	1.63e+003	-0.115
0.1	8	4.86e+003	4.81e+003	490	1.26e+003	0.0951
0.3	10	3.54e+003	3.47e+003	1.17e+003	1.01e+003	0.237
1	10	2.46e+003	2.52e+003	900	811	-0.215

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma^2$

Model A2: $Y_{ij} = Mu(i) + e(ij)$

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```
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-281.447743	5	572.895487
A2	-273.238355	8	562.476711
A3	-278.207838	6	568.415675
fitted	-278.338748	5	566.677496
R	-301.433091	2	606.866183

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs. A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.3895	6	<.0001
Test 2	16.4188	3	0.0009304
Test 3	9.93896	2	0.006947
Test 4	0.261821	1	0.6089

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is less than .1. You may want to consider a different variance model

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

```
Specified effect =          0.1

Risk Type        =     Relative risk

Confidence level =          0.95

             BMD =       0.0205143
```

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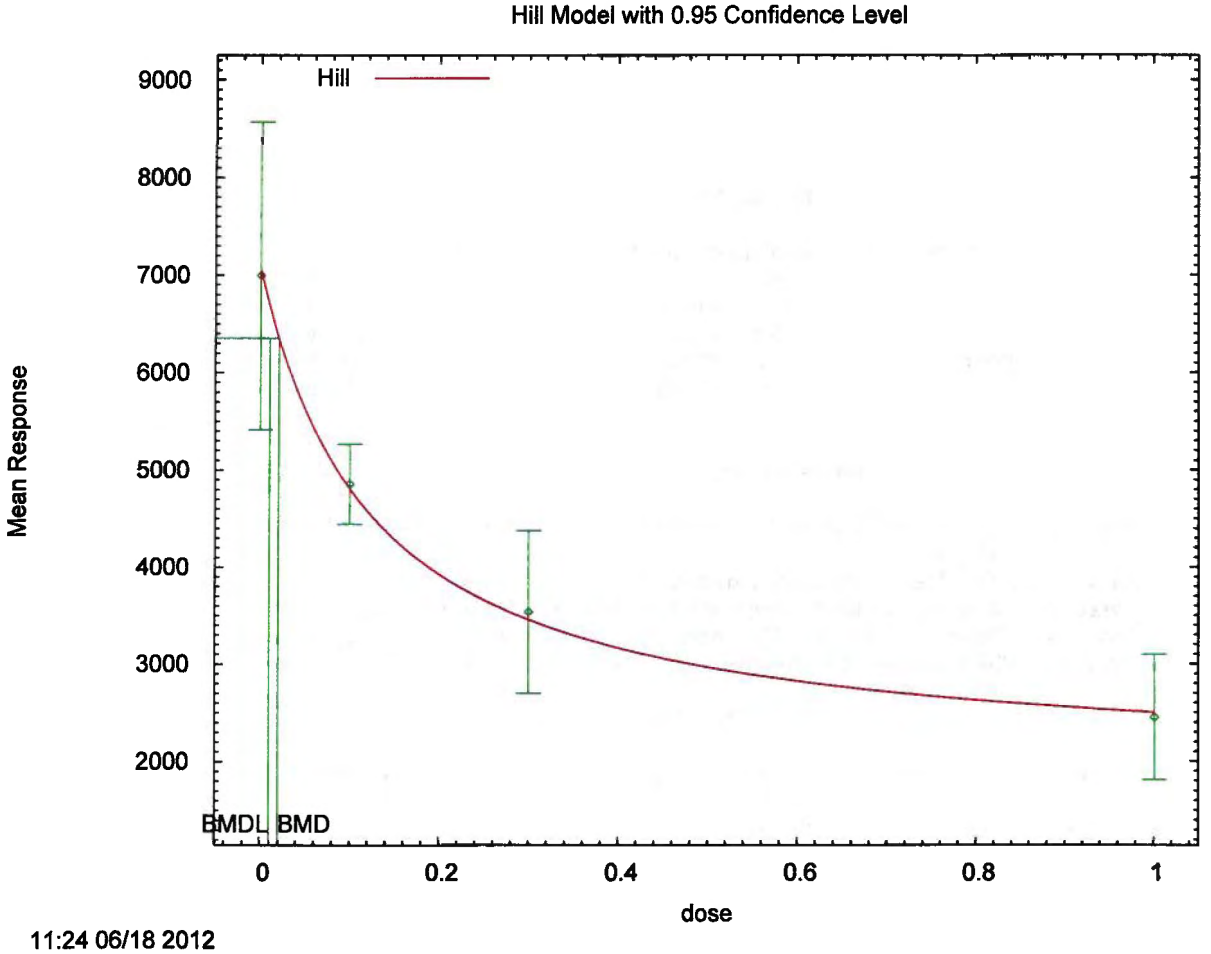
BMDL = 0.0103939



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PND 11 Female Pup BMD Analysis for Brain ChE Inhibition Using Exponential Model

PROPOXUR - PND11 Female Brain
BMDS 2.1.2 - Exponential Model (homogeneous variance model)
BMR = 10%

Data Set: 48784803 acute brain Females PND11

Time	dose	ChE		SD	n
0.5 hr	0	24263	U/L	1220.8	11
0.5 hr	0.1	22320	U/L	1610.7	11
0.5 hr	0.3	16844	U/L	2432.9	11
0.5 hr	1	12592	U/L	2300	11

```
================================================================================
        Exponential Model. (Version: 1.7;  Date: 12/10/2009)
        Input Data File: C:/Usepa/BMDS212/Data/exp_Testrunscontinuous_Setting.(d)
        Gnuplot Plotting File:
                                                    Mon May 07 14:14:11 2012
================================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   rho is set to 0.
   A constant variance model is fit.

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   MLE solution provided: Exact

                                  Initial Parameter Values
```

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Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	15.0613	15.0613	15.0613	15.0613
rho(S)	0	0	0	0
a	14742	14742	25476.2	25476.2
b	0.634777	0.634777	3.13297	3.13297
c	--	--	0.47073	0.47073
d	--	1	--	1

(S) = Specified

Parameter Estimates by Model

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	15.4424	15.4424	15.134	15.0613
rho	0	0	0	0
a	23437.7	23437.7	24649.9	24263
b	0.700996	0.700996	2.75113	3.34891
c	--	--	0.473097	0.518308
d	--	1	--	1.55833

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	11	2.426e+004	1221
0.1	11	2.232e+004	1611
0.3	11	1.684e+004	2433
1	11	1.259e+004	2300

Estimated Values of Interest

Model	Dose	Est Mean	Est Std	Scaled Residual
2	0	2.344e+004	2256	1.213
	0.1	2.185e+004	2256	0.6896
	0.3	1.899e+004	2256	-3.159
	1	1.163e+004	2256	1.419
3	0	2.344e+004	2256	1.213
	0.1	2.185e+004	2256	0.6896
	0.3	1.899e+004	2256	-3.159
	1	1.163e+004	2256	1.419
4	0	2.465e+004	1933	-0.6638
	0.1	2.153e+004	1933	1.362
	0.3	1.735e+004	1933	-0.871
	1	1.249e+004	1933	0.1729
5	0	2.426e+004	1864	-8.431e-008
	0.1	2.232e+004	1864	2.676e-008
	0.3	1.684e+004	1864	-1.391e-007
	1	1.259e+004	1864	1.543e-008

Other models for which likelihoods are calculated:

Model A1: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma^2$

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```
Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-353.3496	5	716.6993
A2	-350.2243	8	716.4485
A3	-353.3496	5	716.6993
R	-396.3873	2	796.7745
2	-361.7322	3	729.4644
3	-361.7322	3	729.4644
4	-354.9483	4	717.8966
5	-353.3496	5	716.6993

Additive constant for all log-likelihoods = -40.43. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

```
Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does Model 2 fit the data? (A3 vs. 2)

Test 5a: Does Model 3 fit the data? (A3 vs. 3)
Test 5b: Is Model 3 better than Model 2? (3 vs. 2)

Test 6a: Does Model 4 fit the data? (A3 vs. 4)
Test 6b: Is Model 4 better than Model 2? (4 vs. 2)

Test 7a: Does Model 5 fit the data? (A3 vs. 5)
Test 7b: Is Model 5 better than Model 3? (5 vs. 3)
Test 7c: Is Model 5 better than Model 4? (5 vs. 4)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	92.33	6	< 0.0001
Test 2	6.251	3	0.1
Test 3	6.251	3	0.1
Test 4	16.77	2	0.0002288
Test 5a	16.77	2	0.0002288
Test 5b	0	0	N/A
Test 6a	3.197	1	0.07376
Test 6b	13.57	1	0.0002301
Test 7a	0	0	N/A
Test 7b	16.77	2	0.0002288
Test 7c	3.197	1	0.07376

38

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 4 is less than .1. Model 2 may not adequately describe the data; you may want to consider another model.

The p-value for Test 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model.

Degrees of freedom for Test 5b are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model.

The p-value for Test 6b is less than .05. Model 4 appears to fit the data better than Model 2.

Degrees of freedom for Test 7a are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 7b is less than .05. Model 5 appears to fit the data better than Model 3.

The p-value for Test 7c is greater than .05. Model 5 does not seem to fit the data better than Model 4.

Benchmark Dose Computations:

Specified Effect = 0.100000

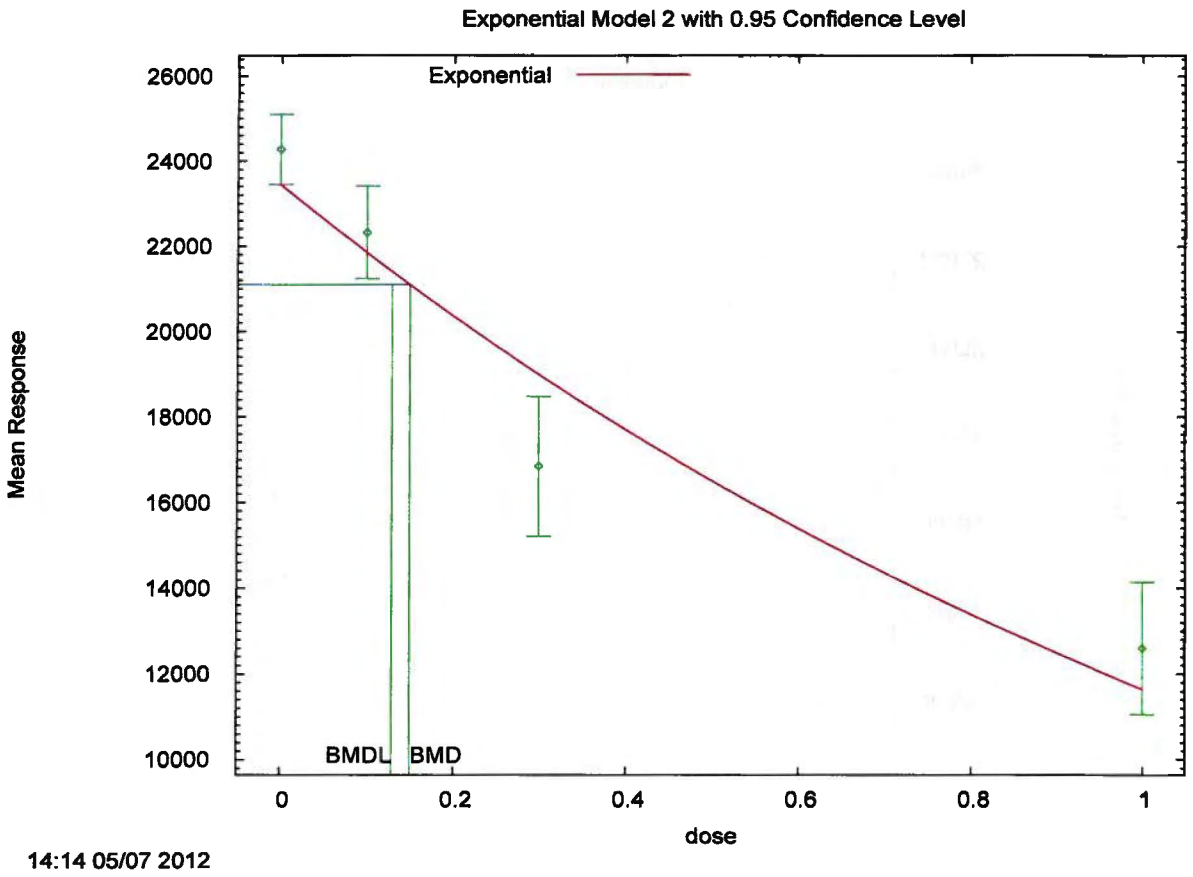
Risk Type = Relative deviation

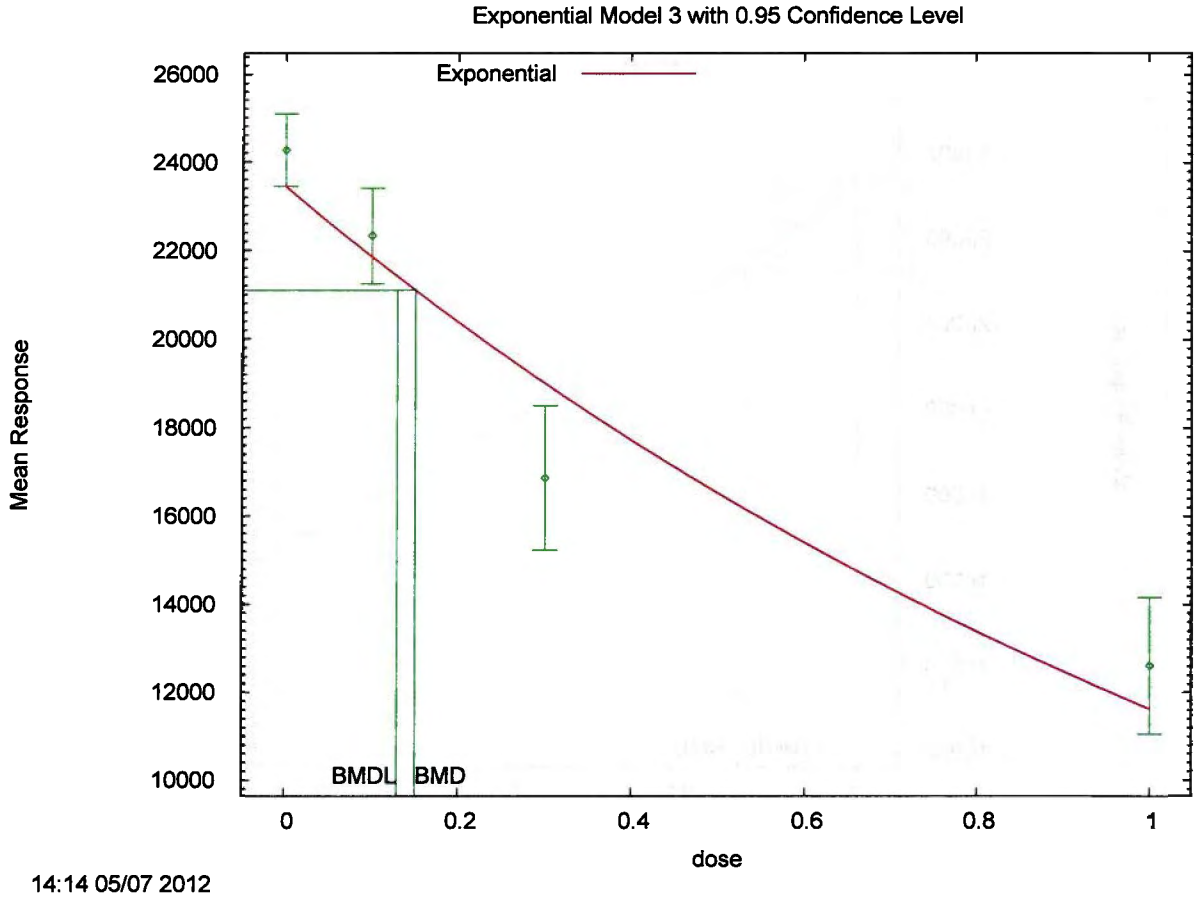
Confidence Level = 0.950000

BMD and BMDL by Model

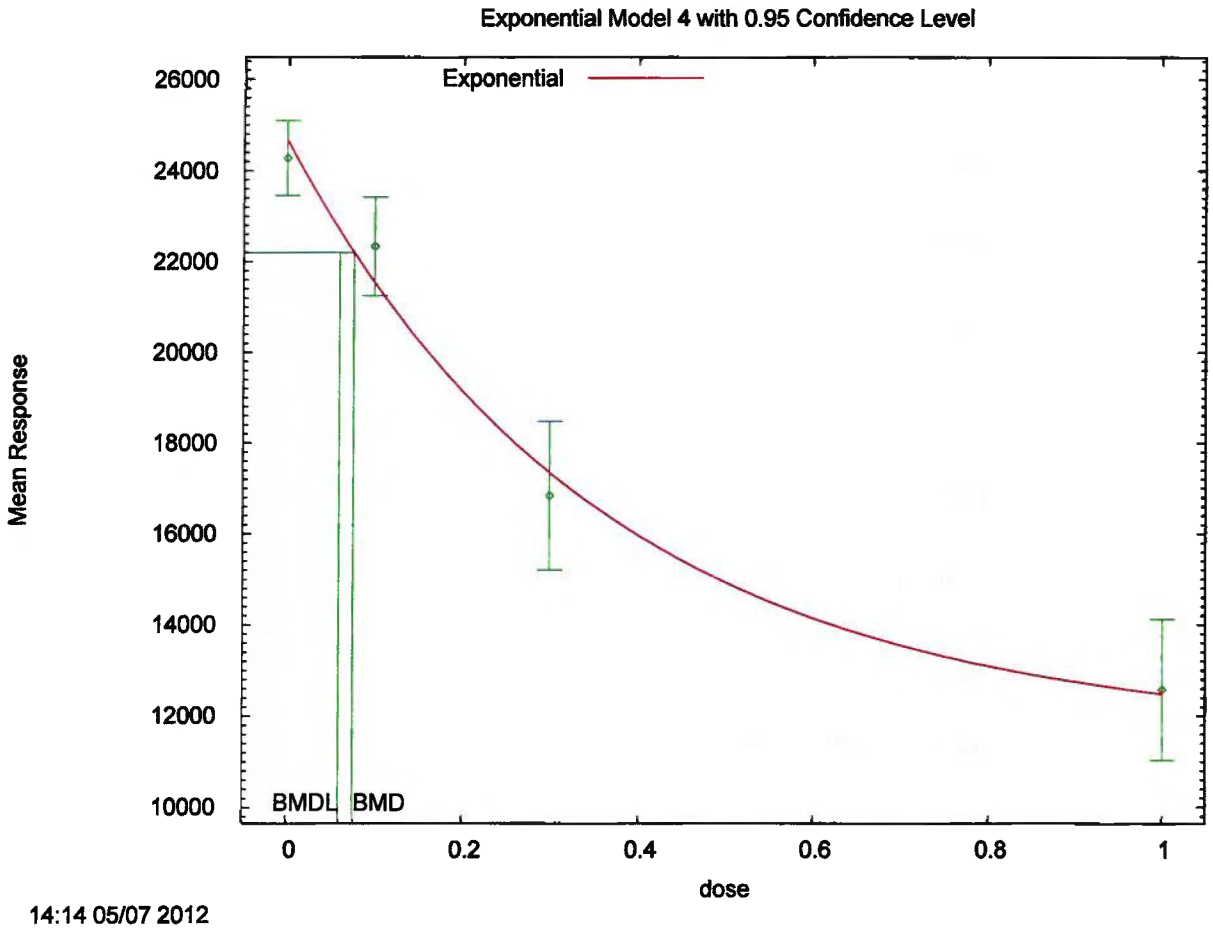
Model	BMD	BMDL	
2	0.150301	0.129508	
3	0.150301	0.129508	
4	0.0764995	0.0600184	p = 0.074
5	0.117152	0.0753261	

39

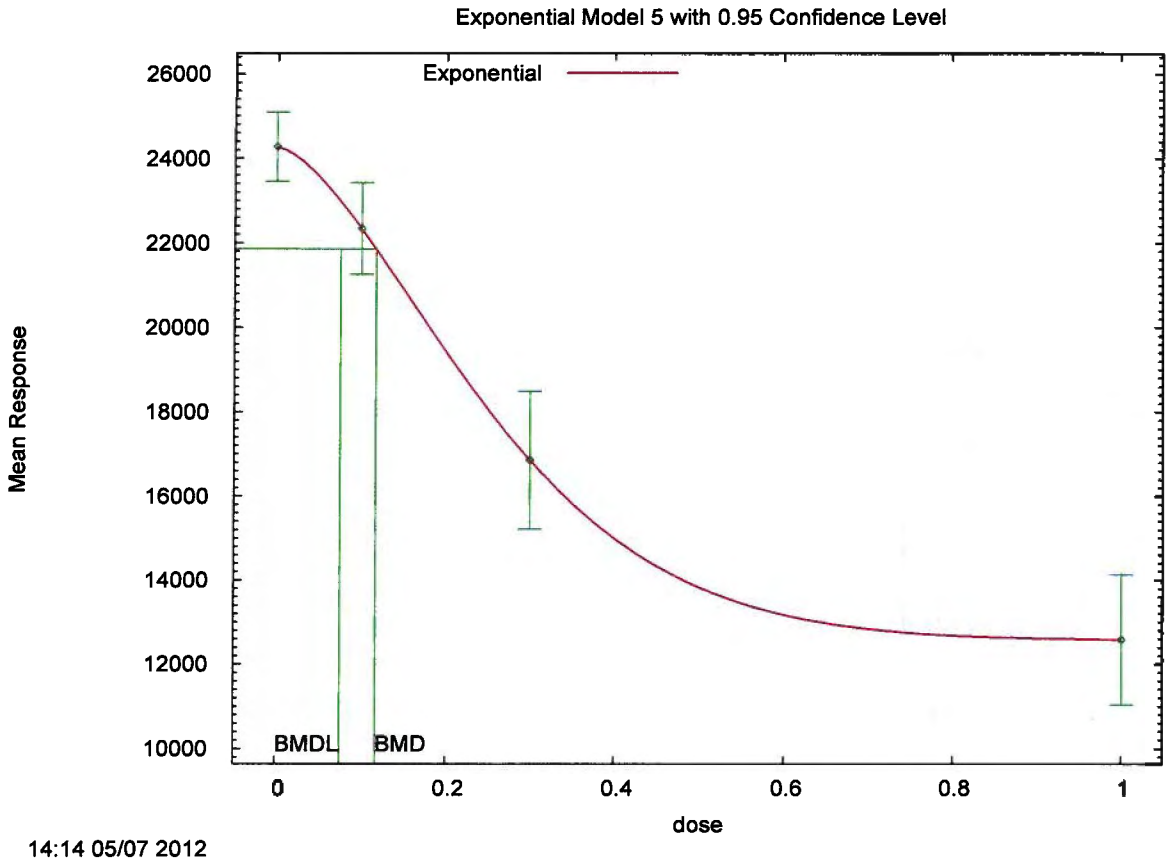

Exponential Model 2 with 0.95 Confidence Level
Exponential
Mean Response
26000
24000
22000
20000
18000
16000
14000
12000
10000
BMDL
BMD
0
0.2
0.4
0.6
0.8
1
dose
14:14 05/07 2012


Exponential Model 3 with 0.95 Confidence Level
Exponential
Mean Response
26000
24000
22000
20000
18000
16000
14000
12000
10000
BMDL
BMD
0
0.2
0.4
0.6
0.8
1
dose
14:14 05/07 2012

41


Exponential Model 4 with 0.95 Confidence Level
Exponential
Mean Response
26000
24000
22000
20000
18000
16000
14000
12000
10000
BMDL
BMD
0
0.2
0.4
0.6
0.8
1
dose
14:14 05/07 2012

42


Exponential Model 5 with 0.95 Confidence Level
Exponential
Mean Response
26000
24000
22000
20000
18000
16000
14000
12000
10000
BMDL
BMD
0
0.2
0.4
0.6
0.8
1
dose
14:14 05/07 2012

43

PND 11 Male Pup BMD Analysis for RBC ChE Inhibition Using Exponential Model

PROPOXUR - PND11 Male RBC
BMDS 2.1.2 - Exponential Model (homogeneous variance model)
BMR = 10%

Data Set: Males PND11 RBC 48784803

	studytype								
	acute	time		timeunit	dose	chei	chunit	sd	n
	acute		0.5	hr	0	6737	U/L	1121.1	9
	acute		0.5	hr	0.1	5916	U/L	986.3	9
4	acute		0.5	hr	0.3	4532	U/L	1319.4	9
			0.5	hr	1	2323	U/L	591.8	8

```
================================================================
        Exponential Model. (Version: 1.7;  Date: 12/10/2009)
        Input Data File: C:/Usepa/BMDS212/Data/exp_Testrunscontinuous_Setting.(d)
        Gnuplot Plotting File:
                                              Mon May 07 11:58:51 2012
================================================================

BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function by Model:
     Model 2:     Y[dose] = a * exp{sign * b * dose}
     Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
     Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

   Note: Y[dose] is the median response for exposure = dose;
         sign = +1 for increasing trend in data;
         sign = -1 for decreasing trend.

     Model 2 is nested within Models 3 and 4.
     Model 3 is nested within Model 5.
     Model 4 is nested within Model 5.


  Dependent variable = Mean
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.

  Total number of dose groups = 4
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	13.7928	13.7928	13.7928	13.7928
rho(S)	0	0	0	0
a	3256.41	3256.41	7073.85	7073.85
b	1.05077	1.05077	1.65247	1.65247
c	--	--	0.164196	0.164196
d	--	1	--	1

(S) = Specified

Parameter Estimates by Model

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	13.8128	13.8128	13.7932	13.7928
rho	0	0	0	0
a	6625.92	6625.92	6753.37	6737
b	1.11739	1.11739	1.77608	1.98588
c	--	--	0.209792	0.251467
d	--	1	--	1.06876

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	9	6737	1121
0.1	9	5916	986.3
0.3	9	4532	1319
1	8	2323	591.8

Estimated Values of Interest

Model	Dose	Est Mean	Est Std	Scaled Residual
2	0	6626	998.6	0.3337
	0.1	5925	998.6	-0.02828
	0.3	4739	998.6	-0.6211
	1	2168	998.6	0.4403
3	0	6626	998.6	0.3337
	0.1	5925	998.6	-0.02828
	0.3	4739	998.6	-0.6211
	1	2168	998.6	0.4403
4	0	6753	988.9	-0.04967
	0.1	5885	988.9	0.09417
	0.3	4549	988.9	-0.05181
	1	2320	988.9	0.007758
5	0	6737	988.7	1.987e-007
	0.1	5916	988.7	-4.962e-007
	0.3	4532	988.7	2.309e-007
	1	2323	988.7	9.523e-007

Other models for which likelihoods are calculated:

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```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
          Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-258.8746	5	527.7493
A2	-256.3498	8	528.6996
A3	-258.8746	5	527.7493
R	-281.9819	2	567.9638
2	-259.224	3	524.4479
3	-259.224	3	524.4479
4	-258.8817	4	525.7634
5	-258.8746	5	527.7493

Additive constant for all log-likelihoods = -32.16. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test 5a: Does Model 3 fit the data? (A3 vs. 3)
Test 5b: Is Model 3 better than Model 2? (3 vs. 2)

Test 6a: Does Model 4 fit the data? (A3 vs. 4)
Test 6b: Is Model 4 better than Model 2? (4 vs. 2)

Test 7a: Does Model 5 fit the data? (A3 vs. 5)
Test 7b: Is Model 5 better than Model 3? (5 vs. 3)
Test 7c: Is Model 5 better than Model 4? (5 vs. 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	51.26	6	< 0.0001
Test 2	5.05	3	0.1682
Test 3	5.05	3	0.1682
Test 4	0.6986	2	0.7052
Test 5a	0.6986	2	0.7052
Test 5b	0	0	N/A
Test 6a	0.01408	1	0.9055
Test 6b	0.6846	1	0.408
Test 7a	1.364e-012	0	N/A

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Test 7b	0.6986	2	0.7052
Test 7c	0.01408	1	0.9055

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

The p-value for Test 5a is greater than .1. Model 3 seems to adequately describe the data.

Degrees of freedom for Test 5b are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

The p-value for Test 6b is greater than .05. Model 4 does not seem to fit the data better than Model 2.

Degrees of freedom for Test 7a are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 7b is greater than .05. Model 5 does not seem to fit the data better than Model 3.

The p-value for Test 7c is greater than .05. Model 5 does not seem to fit the data better than Model 4.

Benchmark Dose Computations:

Specified Effect = 0.100000

Risk Type = Relative deviation

Confidence Level = 0.950000

BMD and BMDL by Model

Model	BMD	BMDL
2	0.0942918	0.0748161
3	0.0942918	0.0748161
4	0.0761809	0.0506134
5	0.0818214	0.0506648

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PND 11 Male Pup BMD Analysis for Brain ChE Inhibition Using Exponential Model

PROPOXUR - PND11 Male Brain
BMDS 2.1.2 - Exponential Model (homogeneous variance model)
BMR = 10%

Data Set: 48784803 acute brain males PND11

Time		Dose	ChE		SD	n
0.5	hr	0	23708	U/L	1480.1	11
0.5	hr	0.1	21887	U/L	1315.5	11
0.5	hr	0.3	18250	U/L	1639.2	11
0.5	hr	1	10594	U/L	1190	11

```
================================================================
        Exponential Model. (Version: 1.7;  Date: 12/10/2009)
        Input Data File: C:/Usepa/BMDS212/Data/exp_Testrunscontinuous_Setting.(d)
        Gnuplot Plotting File:
                                                Mon May 07 12:25:36 2012
================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   rho is set to 0.
   A constant variance model is fit.

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   MLE solution provided: Exact

                                  Initial Parameter Values
```

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	14.4164	14.4164	14.4164	14.4164
rho(S)	0	0	0	0
a	13431.3	13431.3	24893.4	24893.4
b	0.804146	0.804146	1.31733	1.31733
c	--	--	0.212787	0.212787
d	--	1	--	1

(S) = Specified

Parameter Estimates by Model

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	14.43	14.43	14.4197	14.4164
rho	0	0	0	0
a	23640.5	23640.5	23777.2	23708
b	0.814242	0.814242	1.03883	1.44418
c	--	--	0.14148	0.289878
d	--	1	--	1.12009

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	11	2.371e+004	1480
0.1	11	2.189e+004	1316
0.3	11	1.825e+004	1639
1	11	1.059e+004	1190

Estimated Values of Interest

Model	Dose	Est Mean	Est Std	Scaled Residual
2	0	2.364e+004	1360	0.1646
	0.1	2.179e+004	1360	0.232
	0.3	1.852e+004	1360	-0.6513
	1	1.047e+004	1360	0.2972
3	0	2.364e+004	1360	0.1646
	0.1	2.179e+004	1360	0.232
	0.3	1.852e+004	1360	-0.6513
	1	1.047e+004	1360	0.2972
4	0	2.378e+004	1353	-0.1696
	0.1	2.176e+004	1353	0.304
	0.3	1.831e+004	1353	-0.1503
	1	1.059e+004	1353	0.01585
5	0	2.371e+004	1350	-9.875e-008
	0.1	2.189e+004	1350	1.349e-007
	0.3	1.825e+004	1350	1.266e-007
	1	1.059e+004	1350	-1.187e-007

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)

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```
            Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
            Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-339.1604	5	688.3208
A2	-338.5238	8	693.0476
A3	-339.1604	5	688.3208
R	-398.5328	2	801.0656
2	-339.4592	3	684.9183
3	-339.4592	3	684.9183
4	-339.2325	4	686.4651
5	-339.1604	5	688.3208

Additive constant for all log-likelihoods = -40.43. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test 5a: Does Model 3 fit the data? (A3 vs. 3)
Test 5b: Is Model 3 better than Model 2? (3 vs. 2)

Test 6a: Does Model 4 fit the data? (A3 vs. 4)
Test 6b: Is Model 4 better than Model 2? (4 vs. 2)

Test 7a: Does Model 5 fit the data? (A3 vs. 5)
Test 7b: Is Model 5 better than Model 3? (5 vs. 3)
Test 7c: Is Model 5 better than Model 4? (5 vs. 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	120	6	< 0.0001
Test 2	1.273	3	0.7355
Test 3	1.273	3	0.7355
Test 4	0.5975	2	0.7417
Test 5a	0.5975	2	0.7417
Test 5b	1.137e-013	0	N/A
Test 6a	0.1443	1	0.7041
Test 6b	0.4532	1	0.5008
Test 7a	0	0	N/A
Test 7b	0.5975	2	0.7417

50

Test 7c	0.1443	1	0.7041

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

The p-value for Test 5a is greater than .1. Model 3 seems to adequately describe the data.

Degrees of freedom for Test 5b are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

The p-value for Test 6b is greater than .05. Model 4 does not seem to fit the data better than Model 2.

Degrees of freedom for Test 7a are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 7b is greater than .05. Model 5 does not seem to fit the data better than Model 3.

The p-value for Test 7c is greater than .05. Model 5 does not seem to fit the data better than Model 4.

Benchmark Dose Computations:

Specified Effect = 0.100000

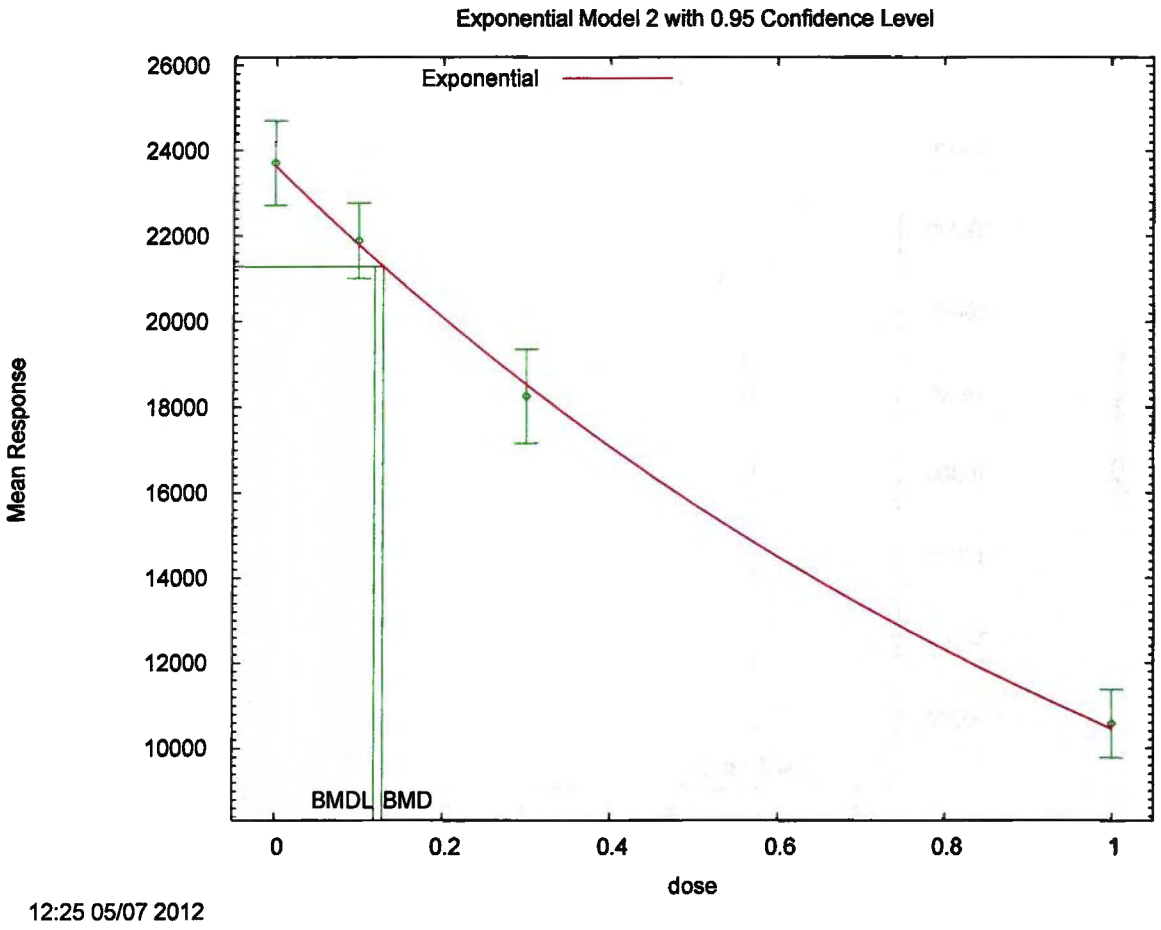
Risk Type = Relative deviation

Confidence Level = 0.950000

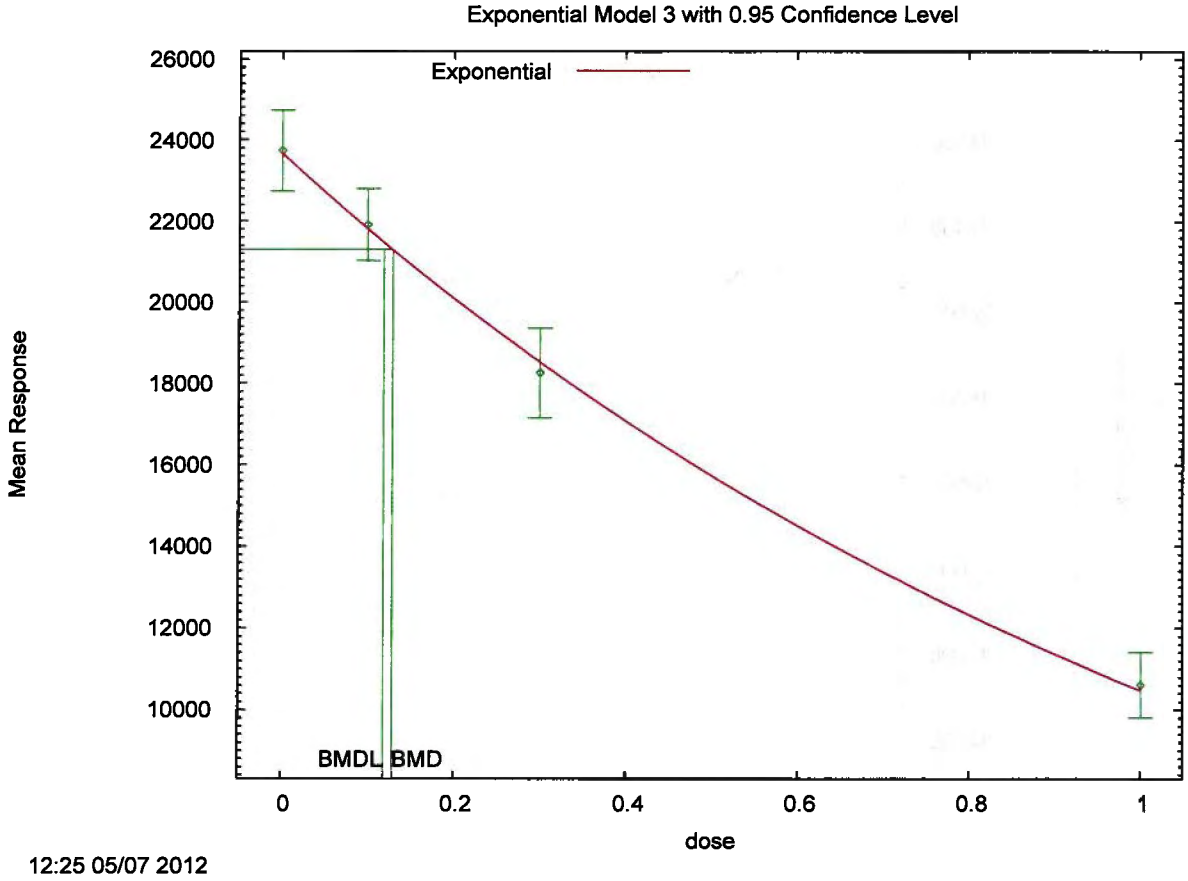
BMD and BMDL by Model

Model	BMD	BMDL
2	0.129397	0.119112
3	0.129397	0.119112
4	0.119211	0.0974144
5	0.128639	0.0979343

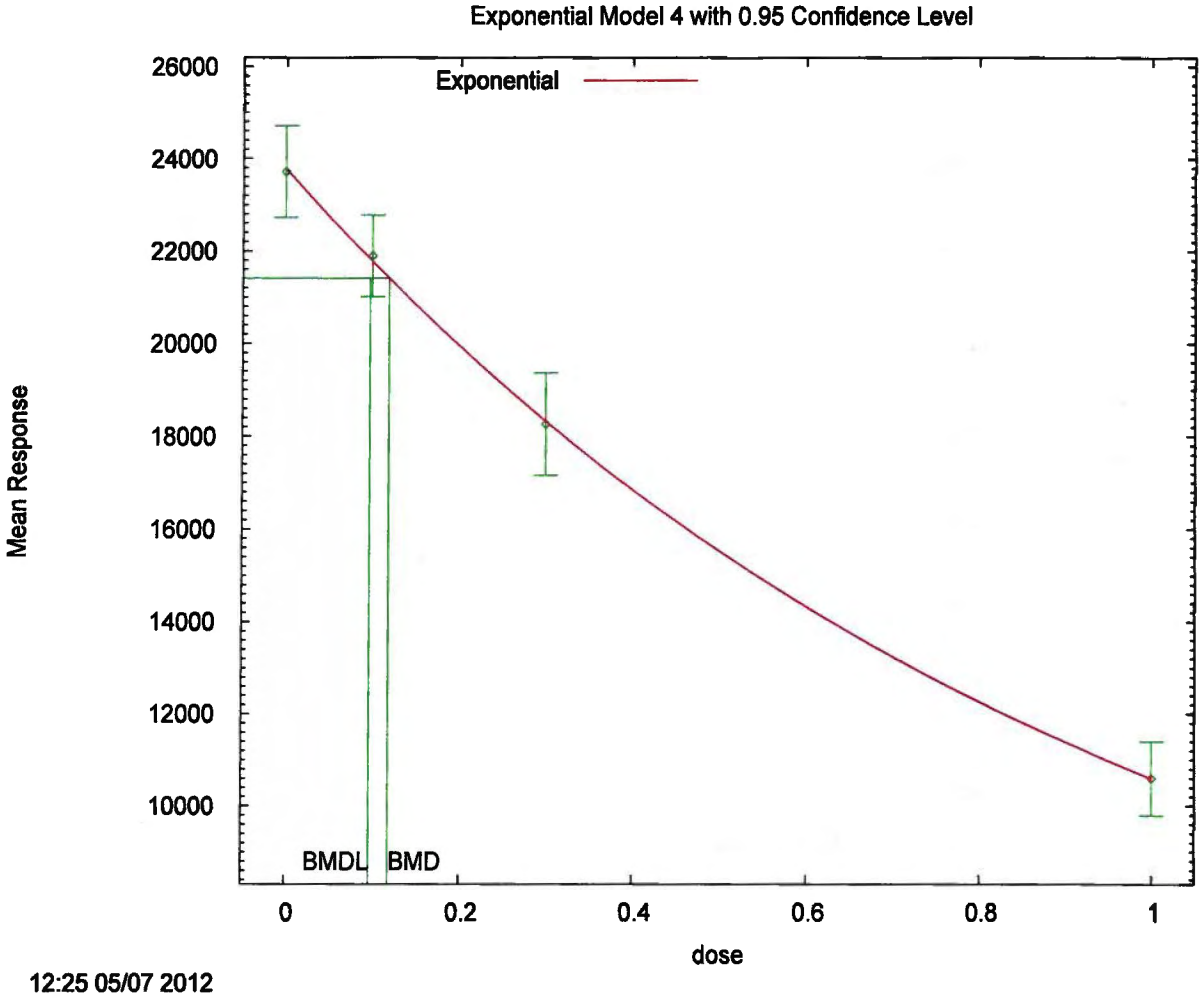
51


Exponential Model 2 with 0.95 Confidence Level
Exponential
Mean Response
26000
24000
22000
20000
18000
16000
14000
12000
10000
BMDL
BMD
0
0.2
0.4
0.6
0.8
1
dose
12:25 05/07 2012

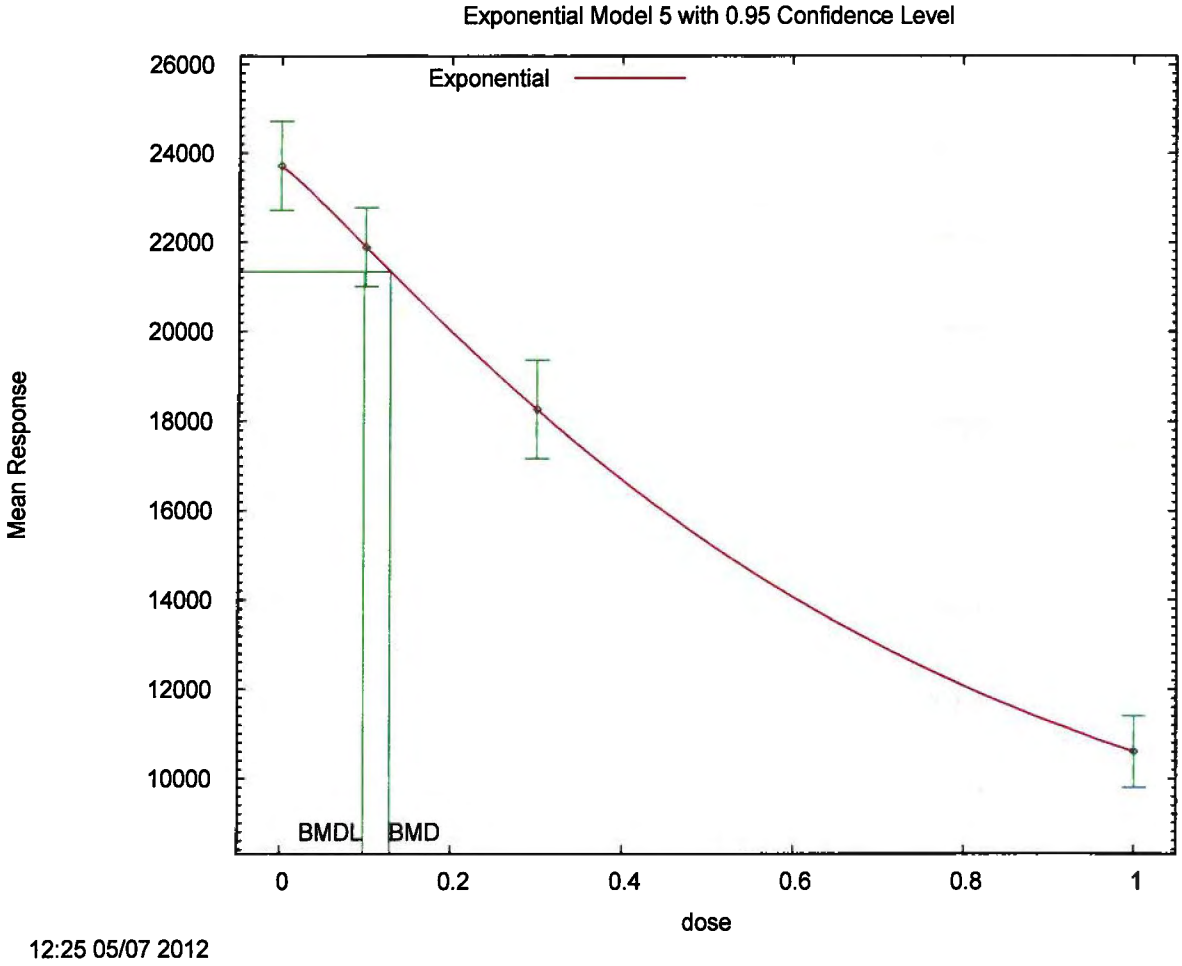
52


Exponential Model 3 with 0.95 Confidence Level
Exponential
Mean Response
26000
24000
22000
20000
18000
16000
14000
12000
10000
BMDL
BMD
0
0.2
0.4
0.6
0.8
1
dose
12:25 05/07 2012

53


Exponential Model 4 with 0.95 Confidence Level
Exponential
Mean Response
26000
24000
22000
20000
18000
16000
14000
12000
10000
BMDL
BMD
0
0.2
0.4
0.6
0.8
1
dose
12:25 05/07 2012

54


Exponential Model 5 with 0.95 Confidence Level
Exponential
Mean Response
26000
24000
22000
20000
18000
16000
14000
12000
10000
BMDL
BMD
0
0.2
0.4
0.6
0.8
1
dose
12:25 05/07 2012

55

Adult Female BMD Analysis for RBC ChE Inhibition Using Exponential Model

PROPOXUR - Adult Female RBC
BMDS 2.1.2 - Exponential Model
BMR = 10%

DataSet: adult female RBC at 0.25 hr post dosing

DOSE	Che	SD	n
0	3220 U/L	894.9	6
1	2697 U/L	728.8	6
2	2158 U/L	630.1	6
3	1515 U/L	645.9	6
5	1246 U/L	427.5	6
10	485 U/L	239.5	6

```
================================================================
        Exponential Model. (Version: 1.7;  Date: 12/10/2009)
        Input Data File: C:/Usepa/BMDS212/Data/exp_Testrunscontinuous_Setting.(d)
        Gnuplot Plotting File:
                                                Thu Jun 07 09:03:13 2012
================================================================

 BMDS Model Run
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   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   MLE solution provided: Exact
```


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Initial Parameter Values

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	2.68472	2.68472	2.68472	2.68472
rho	1.34512	1.34512	1.34512	1.34512
a	831.979	831.979	3381	3381
b	0.187911	0.187911	0.253582	0.253582
c	--	--	0.0717243	0.0717243
d	--	1	--	1

Parameter Estimates by Model

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	2.47268	2.47268	2.32367	2.32367
rho	1.35616	1.35616	1.37493	1.37493
a	3145.43	3145.43	3224.88	3224.88
b	0.192137	0.192137	0.224761	0.224761
c	--	--	0.0507246	0.0507246
d	--	1	--	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	6	3220	894.9
1	6	2697	728.8
2	6	2158	630.1
3	6	1515	645.9
5	6	1246	427.5
10	6	485	239.5

Estimated Values of Interest

Model	Dose	Est Mean	Est Std	Scaled Residual
2	0	3145	810.3	0.2254
	1	2596	711.3	0.3492
	2	2142	624.4	0.06329
	3	1767	548.2	-1.128
	5	1204	422.4	0.2462
	10	460.5	220.2	0.2724
3	0	3145	810.3	0.2254
	1	2596	711.3	0.3492
	2	2142	624.4	0.06329
	3	1767	548.2	-1.128
	5	1204	422.4	0.2462
	10	460.5	220.2	0.2724
4	0	3225	825.2	-0.01447
	1	2609	713.3	0.3034
	2	2116	617.8	0.1646
	3	1723	536.4	-0.9516
	5	1159	408.3	0.5242
	10	487	225	-0.0219
5	0	3225	825.2	-0.01447
	1	2609	713.3	0.3034

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2	2116	617.8	0.1646
3	1723	536.4	-0.9516
5	1159	408.3	0.5242
10	487	225	-0.0219

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model R: Yij = Mu + e(i)
Var{e(ij)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-246.8013	7	507.6026
A2	-241.7651	12	507.5301
A3	-242.095	8	500.1899
R	-269.4793	2	542.9587
2	-242.6912	4	493.3823
3	-242.6912	4	493.3823
4	-242.5467	5	495.0933
5	-242.5467	5	495.0933

Additive constant for all log-likelihoods = -33.08. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test 5a: Does Model 3 fit the data? (A3 vs. 3)
Test 5b: Is Model 3 better than Model 2? (3 vs. 2)

Test 6a: Does Model 4 fit the data? (A3 vs. 4)
Test 6b: Is Model 4 better than Model 2? (4 vs. 2)

Test 7a: Does Model 5 fit the data? (A3 vs. 5)
Test 7b: Is Model 5 better than Model 3? (5 vs. 3)
Test 7c: Is Model 5 better than Model 4? (5 vs. 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value

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Test 1	55.43	10	< 0.0001
Test 2	10.07	5	0.07321
Test 3	0.6598	4	0.9562
Test 4	1.192	4	0.8793
Test 5a	1.192	4	0.8793
Test 5b	1.705e-013	0	N/A
Test 6a	0.9034	3	0.8246
Test 6b	0.289	1	0.5909
Test 7a	0.9034	3	0.8246
Test 7b	0.289	1	0.5909
Test 7c	-1.137e-013	0	N/A

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

The p-value for Test 5a is greater than .1. Model 3 seems to adequately describe the data.

Degrees of freedom for Test 5b are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

The p-value for Test 6b is greater than .05. Model 4 does not seem to fit the data better than Model 2.

The p-value for Test 7a is greater than .1. Model 5 seems to adequately describe the data.

The p-value for Test 7b is greater than .05. Model 5 does not seem to fit the data better than Model 3.

Degrees of freedom for Test 7c are less than or equal to 0. The Chi-Square test for fit is not valid.

Benchmark Dose Computations:

Specified Effect = 0.100000

Risk Type = Relative deviation

Confidence Level = 0.950000

BMD and BMDL by Model

Model	BMD	BMDL
2	0.548362	0.455429
3	0.548362	0.455429

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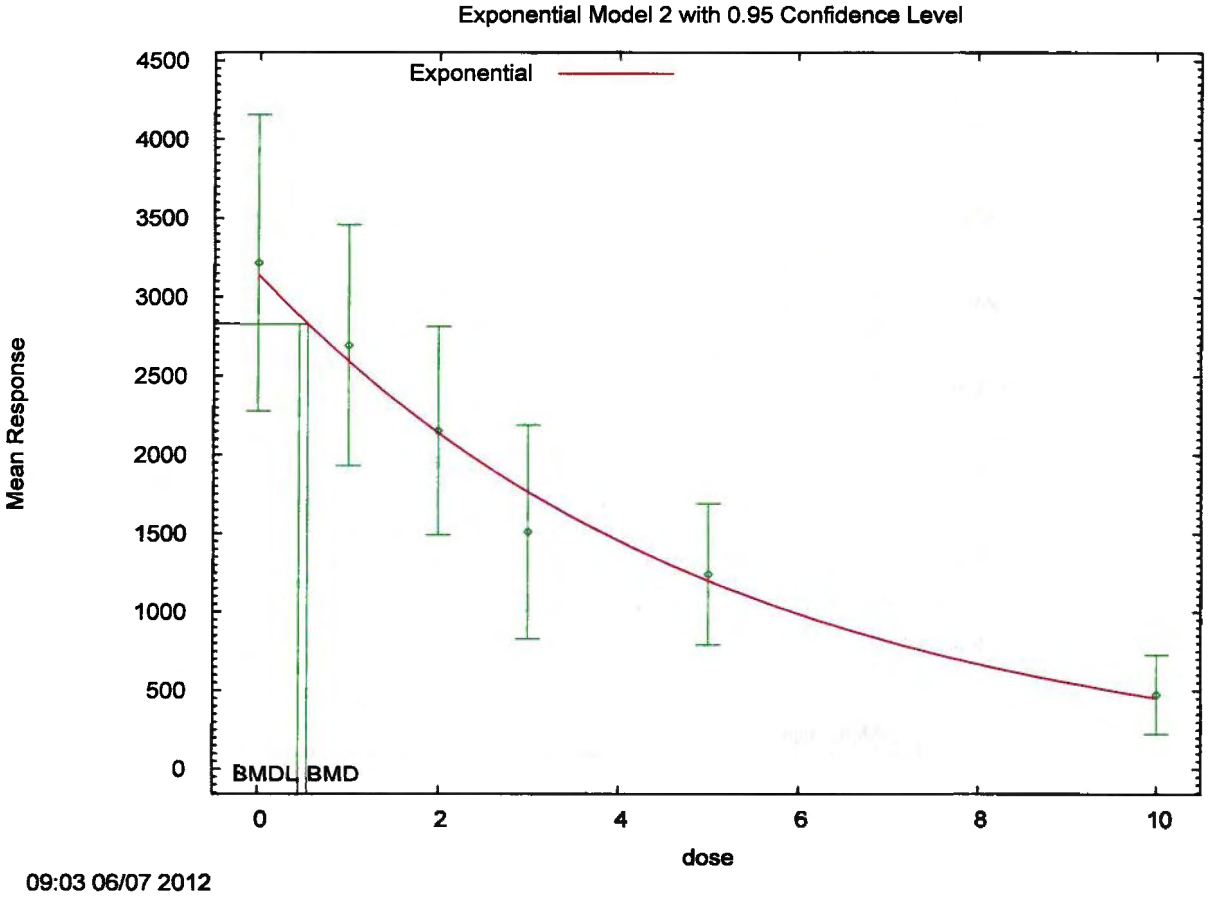
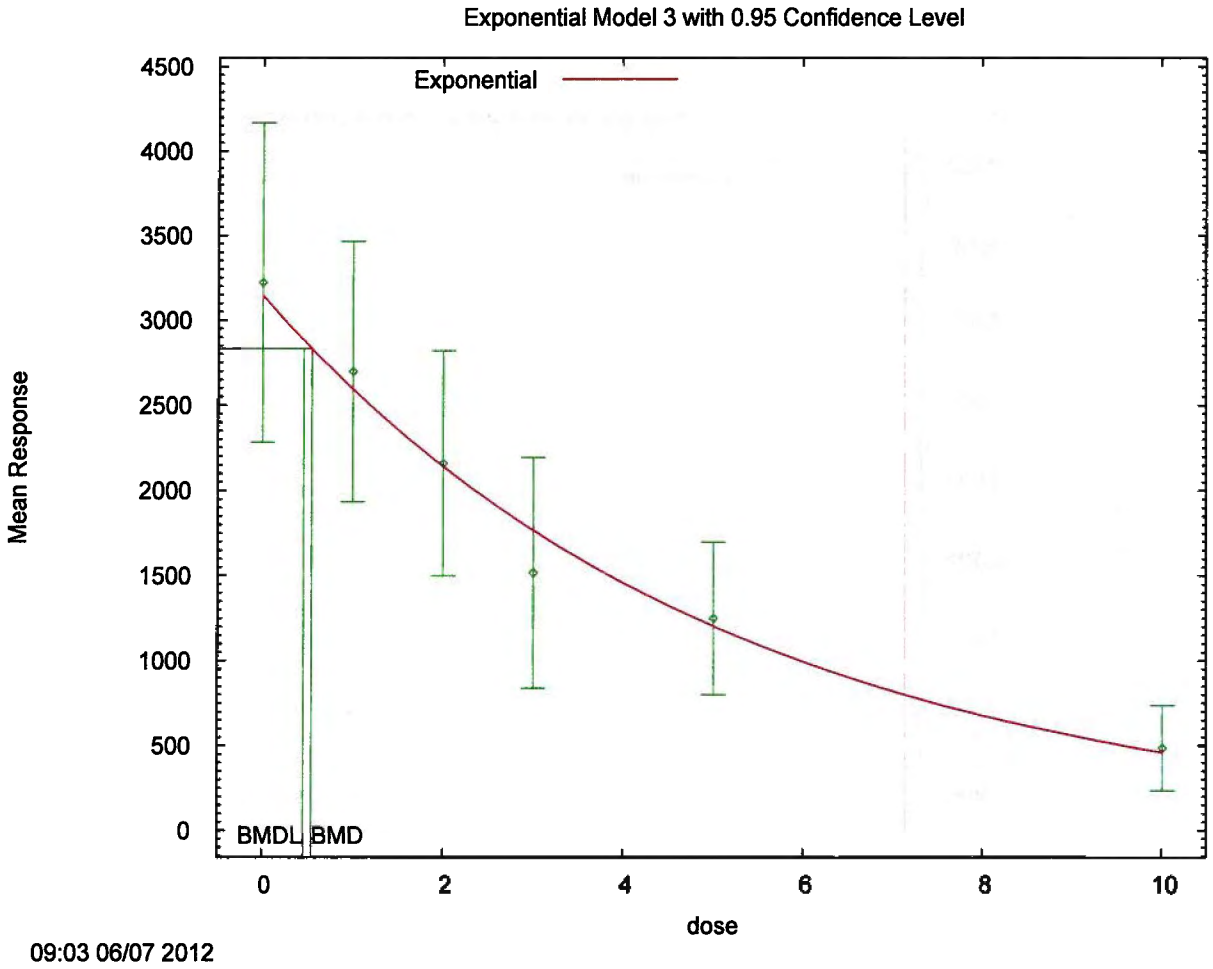
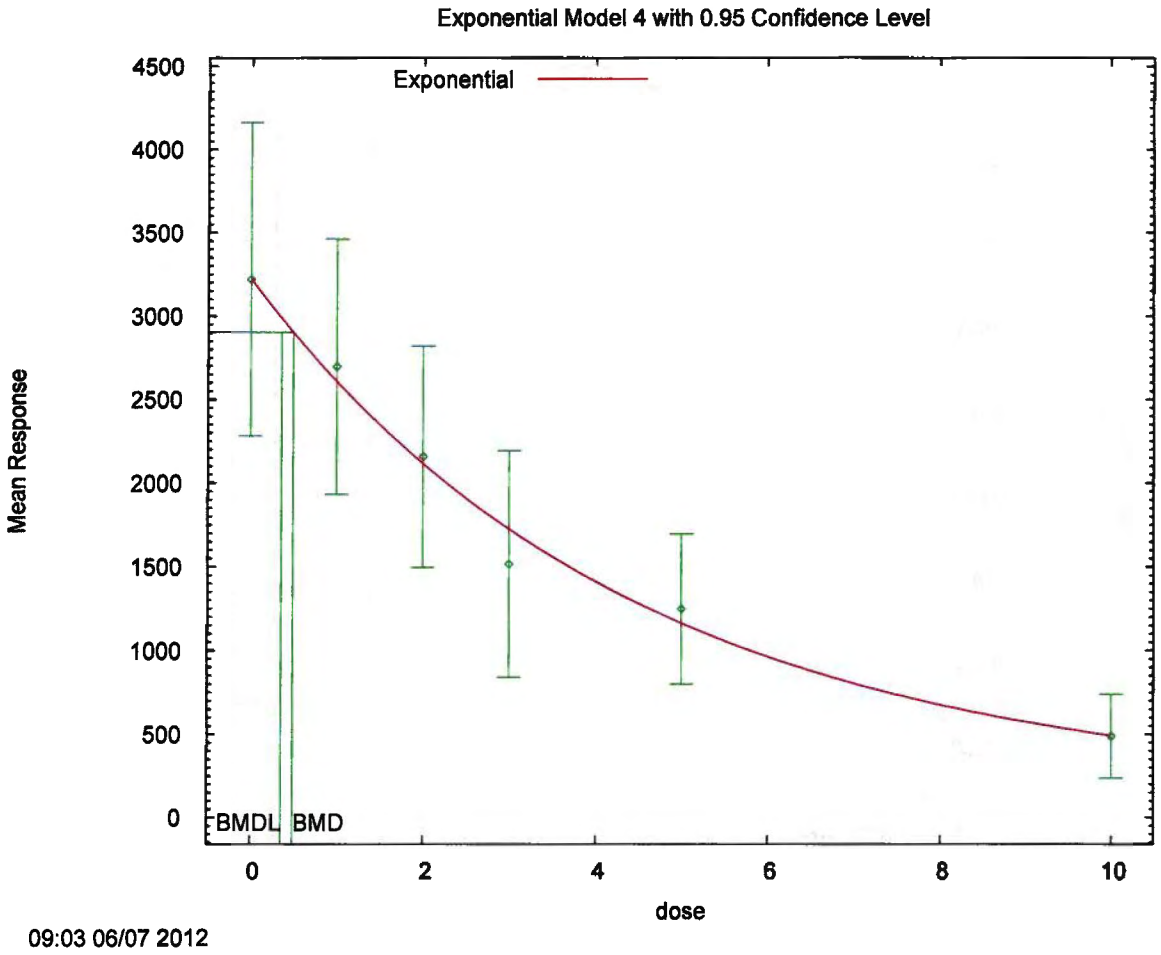
4	0.495262	0.360857
5	0.495262	0.360857

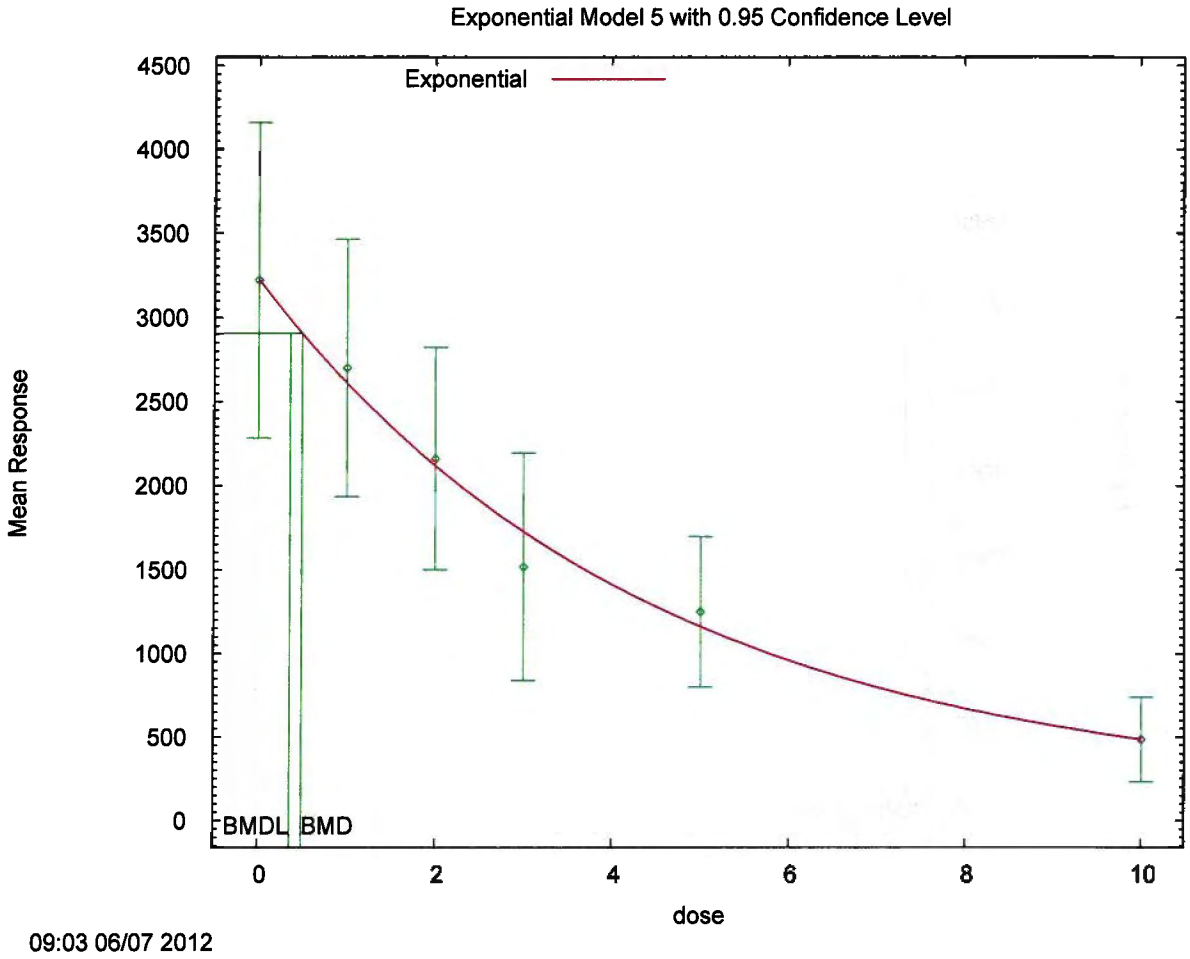


60


Exponential Model 3 with 0.95 Confidence Level
Exponential
Mean Response
4500
4000
3500
3000
2500
2000
1500
1000
500
0
BMDL
BMD
0
2
4
6
8
10
dose
09:03 06/07 2012


Exponential Model 4 with 0.95 Confidence Level
Exponential
Mean Response
4500
4000
3500
3000
2500
2000
1500
1000
500
0
BMDL
BMD
0
2
4
6
8
10
dose
09:03 06/07 2012

62


Exponential Model 5 with 0.95 Confidence Level
Exponential
Mean Response
4500
4000
3500
3000
2500
2000
1500
1000
500
0
BMDL
BMD
0
2
4
6
8
10
dose
09:03 06/07 2012

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Adult Female BMD Analysis for Brain ChE Inhibition Using Exponential Model

BMDS 2.1.2 - Exponential Model (nonhomogeneous variance – best fit)

BMR = 10%

Dataset: acute brain female adult at 0.25 hrs post dosing

Dose	ChE		SD	n
0	51558	U/L	1322.9	6
1	46481	U/L	2540.1	6
2	42136	U/L	5139.1	6
3	34790	U/L	2268.7	6
5	26276	U/L	6965.7	6
10	24324	U/L	13626.8	6

```
================================================================
        Exponential Model. (Version: 1.7;  Date: 12/10/2009)
        Input Data File: C:/Usepa/BMDS212/Data/exp_Testrunscontinuous_Setting.(d)
        Gnuplot Plotting File:
                                                Thu Jun 07 12:33:27 2012
================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   MLE solution provided: Exact


                              Initial Parameter Values

    Variable          Model 2          Model 3          Model 4          Model 5
    --------          -------          -------          -------          -------
```


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lnalpha	65.7985	65.7985	65.7985	65.7985
rho	-4.69136	-4.69136	-4.69136	-4.69136
a	27502.1	27502.1	54135.9	54135.9
b	0.0784062	0.0784062	0.349327	0.349327
c	--	--	0.427918	0.427918
d	--	1	--	1

Parameter Estimates by Model

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	53.1801	51.8956	63.3822	64.1543
rho	-3.48949	-3.36982	-4.44667	-4.52536
a	51893.7	51832.1	51979.7	51579.9
b	0.120147	0.124256	0.184354	0.273658
c	--	--	0.288445	0.421209
d	--	1.03317	--	1.34443

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	6	5.156e+004	1323
1	6	4.648e+004	2540
2	6	4.214e+004	5139
3	6	3.479e+004	2269
5	6	2.628e+004	6966
10	6	2.432e+004	1.363e+004

Estimated Values of Interest

Model	Dose	Est Mean	Est Std	Scaled Residual
2	0	5.189e+004	2095	-0.3925
	1	4.602e+004	2584	0.4381
	2	4.081e+004	3187	1.02
	3	3.619e+004	3930	-0.8721
	5	2.846e+004	5976	-0.8947
	10	1.561e+004	1.705e+004	1.253
3	0	5.183e+004	2115	-0.3174
	1	4.616e+004	2571	0.3083
	2	4.088e+004	3155	0.973
	3	3.613e+004	3884	-0.8478
	5	2.812e+004	5927	-0.7619
	10	1.483e+004	1.742e+004	1.335
4	0	5.198e+004	1898	-0.5441
	1	4.575e+004	2521	0.7076
	2	4.057e+004	3293	1.162
	3	3.627e+004	4226	-0.8563
	5	2.971e+004	6586	-1.276
	10	2.085e+004	1.447e+004	0.5885
5	0	5.158e+004	1854	-0.02887
	1	4.678e+004	2312	-0.3207
	2	4.086e+004	3140	0.9933
	3	3.559e+004	4293	-0.4562
	5	2.823e+004	7253	-0.6589
	10	2.235e+004	1.23e+004	0.3934

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Other models for which likelihoods are calculated:

Model A1: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma^2$

Model A2: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma(i)^2$

Model A3: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = exp(lalpha + log(mean(i)) * rho)$

Model R: $Yij = Mu + e(i)$
$Var\{e(ij)\} = Sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-332.1801	7	678.3602
A2	-312.7243	12	649.4486
A3	-317.7667	8	651.5333
R	-355.5205	2	715.041
2	-319.7208	4	647.4416
3	-319.6983	5	649.3966
4	-319.2167	5	648.4333
5	-317.9674	6	647.9348

Additive constant for all log-likelihoods = -33.08. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test 5a: Does Model 3 fit the data? (A3 vs. 3)
Test 5b: Is Model 3 better than Model 2? (3 vs. 2)

Test 6a: Does Model 4 fit the data? (A3 vs. 4)
Test 6b: Is Model 4 better than Model 2? (4 vs. 2)

Test 7a: Does Model 5 fit the data? (A3 vs. 5)
Test 7b: Is Model 5 better than Model 3? (5 vs. 3)
Test 7c: Is Model 5 better than Model 4? (5 vs. 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	85.59	10	< 0.0001
Test 2	38.91	5	< 0.0001
Test 3	10.08	4	0.03902
Test 4	3.908	4	0.4186
Test 5a	3.863	3	0.2766

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Test 5b	0.04502	1	0.832
Test 6a	2.9	3	0.4073
Test 6b	1.008	1	0.3153
Test 7a	0.4015	2	0.8181
Test 7b	3.462	1	0.0628
Test 7c	2.499	1	0.114

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

The p-value for Test 5a is greater than .1. Model 3 seems to adequately describe the data.

The p-value for Test 5b is greater than .05. Model 3 does not seem to fit the data better than Model 2.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

The p-value for Test 6b is greater than .05. Model 4 does not seem to fit the data better than Model 2.

The p-value for Test 7a is greater than .1. Model 5 seems to adequately describe the data.

The p-value for Test 7b is greater than .05. Model 5 does not seem to fit the data better than Model 3.

The p-value for Test 7c is greater than .05. Model 5 does not seem to fit the data better than Model 4.

Benchmark Dose Computations:

Specified Effect = 0.100000

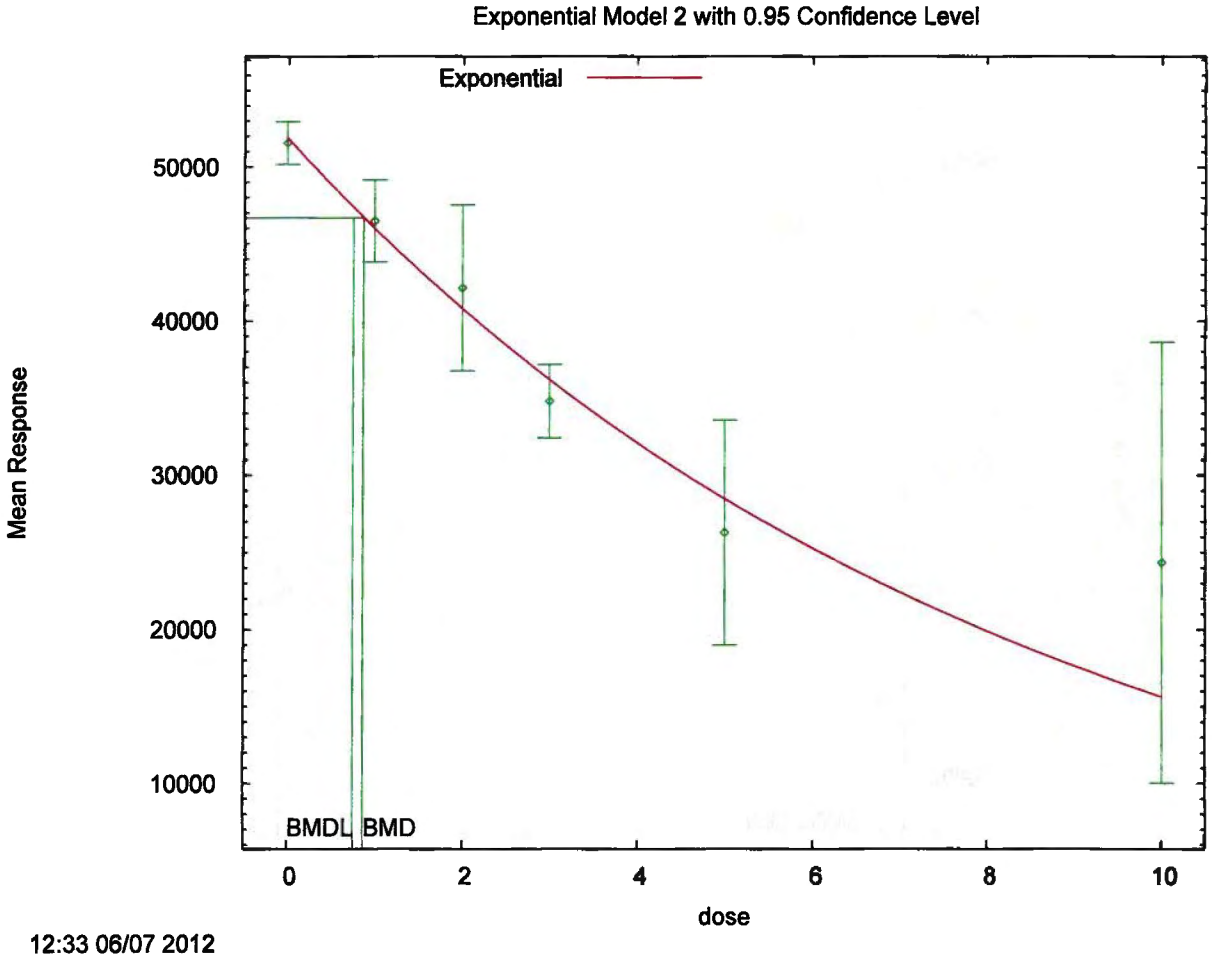
Risk Type = Relative deviation

Confidence Level = 0.950000

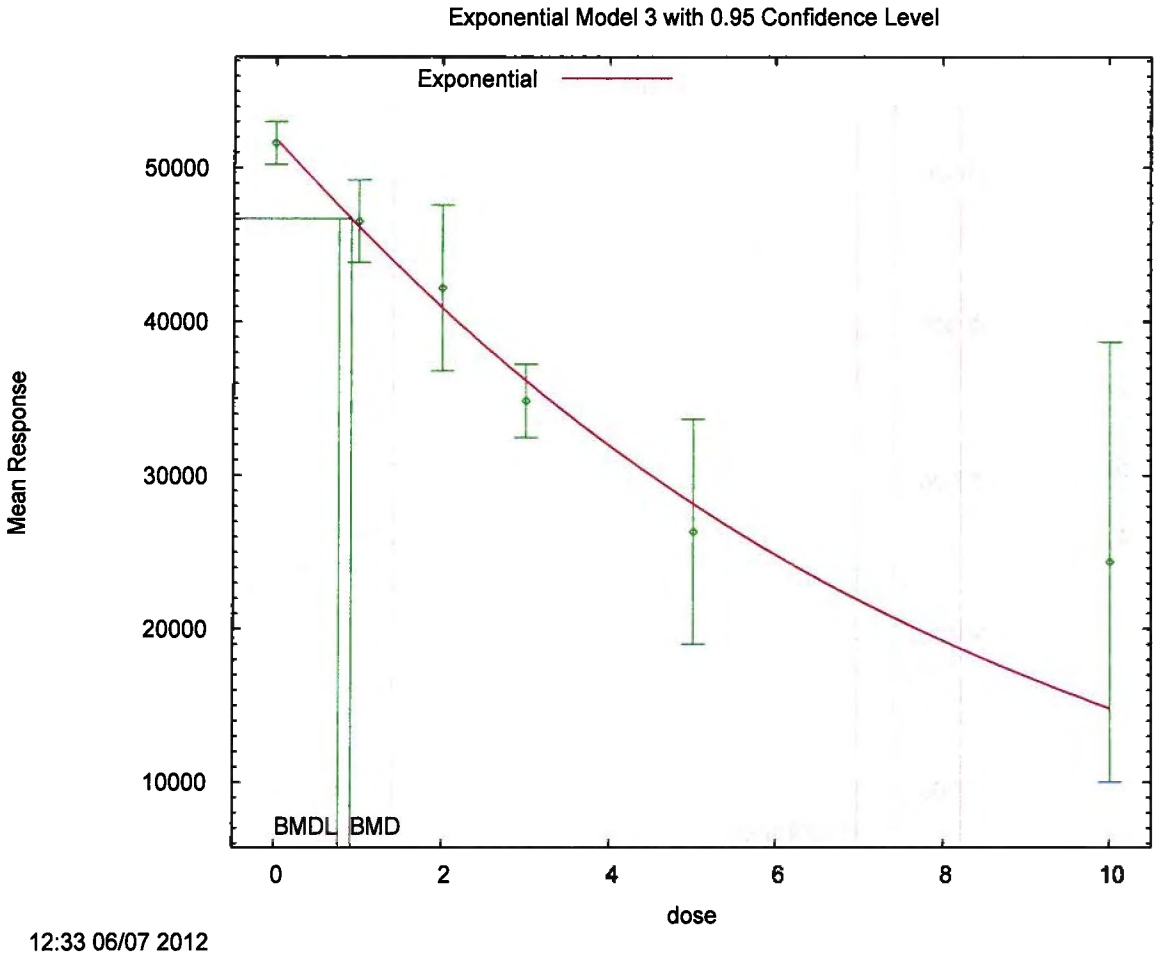
BMD and BMDL by Model

Model	BMD	BMDL
2	0.876932	0.76335
3	0.911454	0.764225
4	0.821507	0.681906
5	1.06114	0.774727

67


Exponential Model 2 with 0.95 Confidence Level
Exponential
Mean Response
50000
40000
30000
20000
10000
BMDL
BMD
0
2
4
6
8
10
dose
12:33 06/07 2012

68


Exponential Model 3 with 0.95 Confidence Level
Exponential
Mean Response
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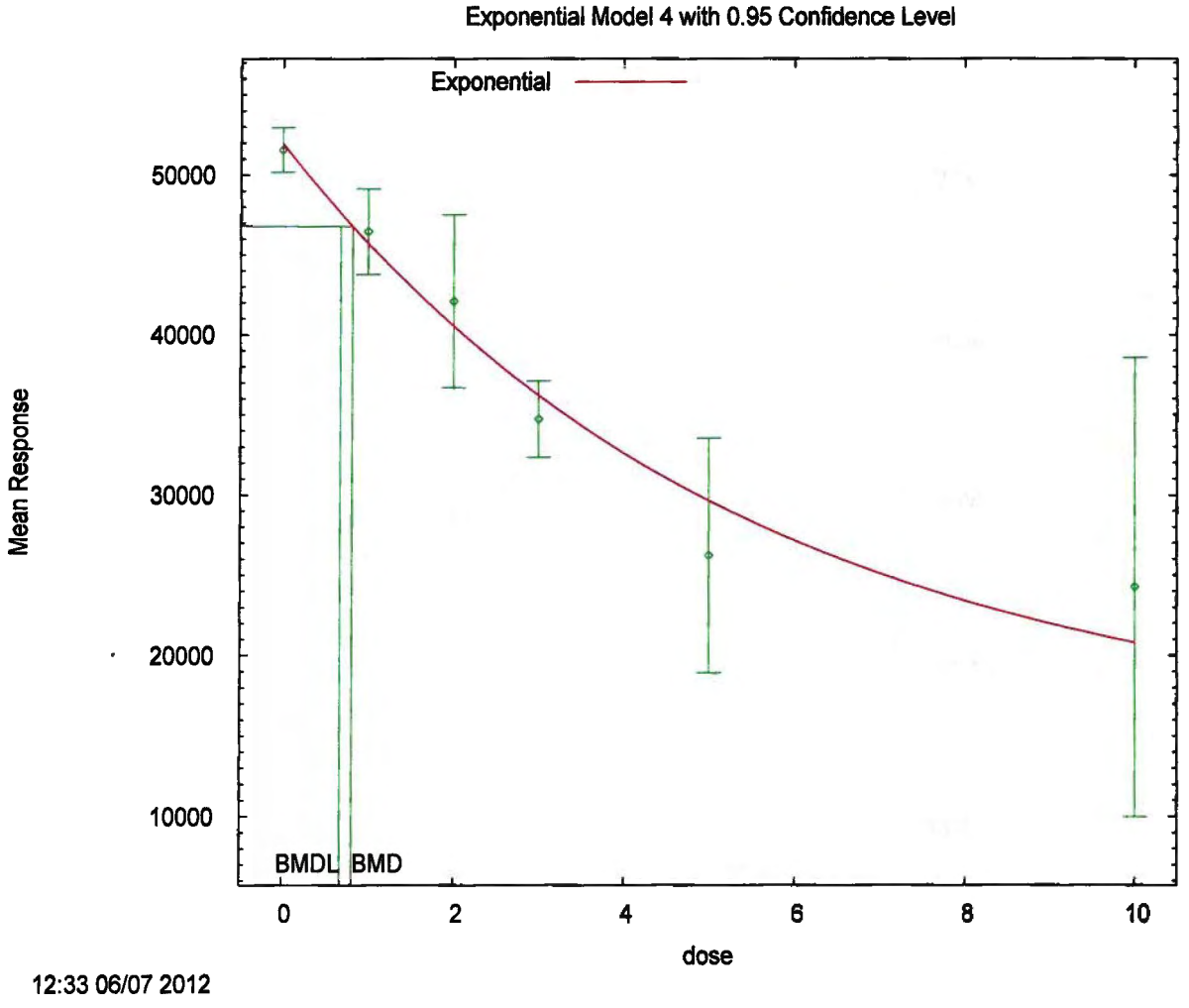
30000
20000
10000
BMDL
BMD
0
2
4
6
8
10
dose
12:33 06/07 2012

69


Exponential Model 4 with 0.95 Confidence Level
Exponential
Mean Response
50000
40000
30000
20000
10000
BMDL
BMD
0
2
4
6
8
10
dose
12:33 06/07 2012

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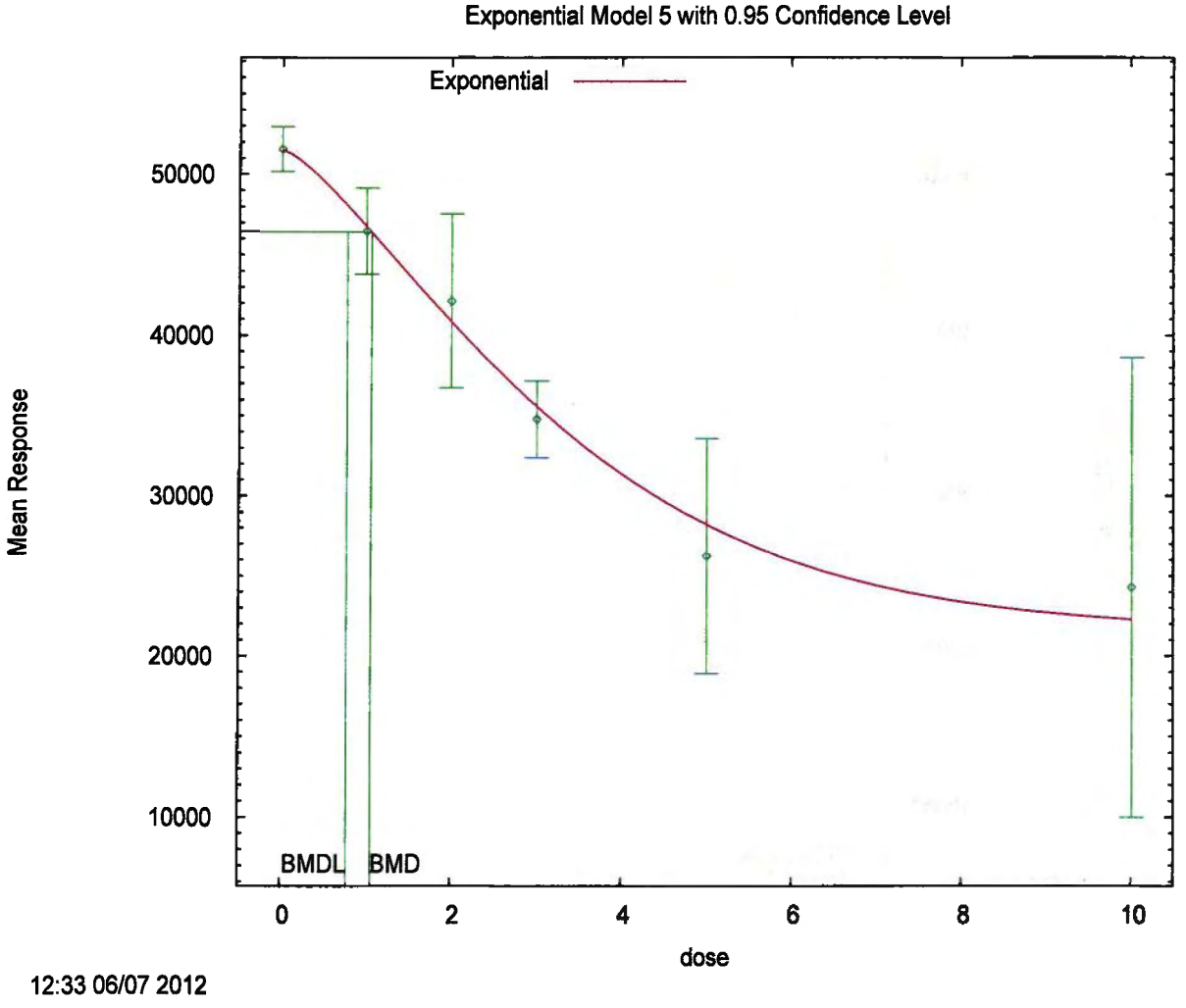
Exponential Model 5 with 0.95 Confidence Level
Exponential
Mean Response
50000
40000
30000
20000
10000
BMDL
BMD
0
2
4
6
8
10
dose
12:33 06/07 2012

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PROPOXUR - Adult Male RBC **Note: high dose (10 mg/kg/day) dropped since there was no acceptable BMD fit**

BMDS 2.12 - Exponential Model

BMR = 10%

dose	chei	chunit	sd	n
0	2928	U/L	1187.6	6
1	2499	U/L	468.4	6
2	2061	U/L	792 .5	6
3	1701	U/L	934.8	6
5	1453	U/L	408.5	6

```
================================================================
        Exponential Model. (Version: 1.7;  Date: 12/10/2009)
        Input Data File: C:/Usepa/BMDS212/Data/exp_Testrunscontinuous_Setting.(d)
        Gnuplot Plotting File:
                                              Mon Jun 11 12:38:17 2012
================================================================

BMDS Model Run
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  The form of the response function by Model:
     Model 2:     Y[dose] = a * exp{sign * b * dose}
     Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
     Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

   Note: Y[dose] is the median response for exposure = dose;
         sign = +1 for increasing trend in data;
         sign = -1 for decreasing trend.

     Model 2 is nested within Models 3 and 4.
     Model 3 is nested within Model 5.
     Model 4 is nested within Model 5.


  Dependent variable = Mean
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  MLE solution provided: Exact

                              Initial Parameter Values

    Variable          Model 2          Model 3          Model 4          Model 5
    --------          -------          -------          -------          -------
```


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lnalpha	1.59226	1.59226	1.59226	1.59226
rho	1.50831	1.50831	1.50831	1.50831
a	1500.99	1500.99	3074.4	3074.4
b	0.144329	0.144329	0.254213	0.254213
c	--	--	0.236306	0.236306
d	--	1	--	1

Parameter Estimates by Model

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	-1.94991	117.185	-0.925051	-0.925052
rho	1.97589	-13.5129	1.8413	1.8413
a	2834.45	2128.4	2913.48	2913.48
b	0.144133	0.0603954	0.251355	0.251355
c	--	--	0.275837	0.275837
d	--	17.4896	--	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	6	2928	1188
1	6	2499	468.4
2	6	2061	792.5
3	6	1701	934.8
5	6	1453	408.5

Estimated Values of Interest

Model	Dose	Est Mean	Est Std	Scaled Residual
2	0	2834	971.5	0.2359
	1	2454	842.5	0.1308
	2	2125	730.7	-0.2132
	3	1839	633.7	-0.535
	5	1379	476.7	0.3815
3	0	2128	913.1	2.145
	1	2128	913.1	0.9942
	2	2128	913.1	-0.1808
	3	2128	913.1	-1.147
	5	2128	913.1	-1.812
4	0	2913	974.2	0.0365
	1	2445	828.9	0.1609
	2	2080	714.3	-0.06469
	3	1796	624.1	-0.3737
	5	1404	497.5	0.2411
5	0	2913	974.2	0.0365
	1	2445	828.9	0.1609
	2	2080	714.3	-0.06469
	3	1796	624.1	-0.3737
	5	1404	497.5	0.2411

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)

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```
            Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
            Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-213.2586	6	438.5172
A2	-208.8074	10	437.6147
A3	-211.7294	7	437.4588
R	-219.5058	2	443.0117
2	-211.9663	4	431.9327
3	-219.5058	5	449.0117
4	-211.9129	5	433.8259
5	-211.9129	5	433.8259

Additive constant for all log-likelihoods = -27.57. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test 5a: Does Model 3 fit the data? (A3 vs. 3)
Test 5b: Is Model 3 better than Model 2? (3 vs. 2)

Test 6a: Does Model 4 fit the data? (A3 vs. 4)
Test 6b: Is Model 4 better than Model 2? (4 vs. 2)

Test 7a: Does Model 5 fit the data? (A3 vs. 5)
Test 7b: Is Model 5 better than Model 3? (5 vs. 3)
Test 7c: Is Model 5 better than Model 4? (5 vs. 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	21.4	8	0.006164
Test 2	8.903	4	0.06358
Test 3	5.844	3	0.1194
Test 4	0.4739	3	0.9246
Test 5a	15.55	2	0.0004195
Test 5b	-15.08	1	N/A
Test 6a	0.367	2	0.8323
Test 6b	0.1068	1	0.7438
Test 7a	0.367	2	0.8323
Test 7b	15.19	0	N/A

74

Test 7c	-5.684e-014	0	N/A

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

The p-value for Test 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model.

The p-value for Test 5b is less than .05. Model 3 appears to fit the data better than Model 2.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

The p-value for Test 6b is greater than .05. Model 4 does not seem to fit the data better than Model 2.

The p-value for Test 7a is greater than .1. Model 5 seems to adequately describe the data.

Degrees of freedom for Test 7b are less than or equal to 0. The Chi-Square test for fit is not valid.

Degrees of freedom for Test 7c are less than or equal to 0. The Chi-Square test for fit is not valid.

Benchmark Dose Computations:

Specified Effect = 0.100000

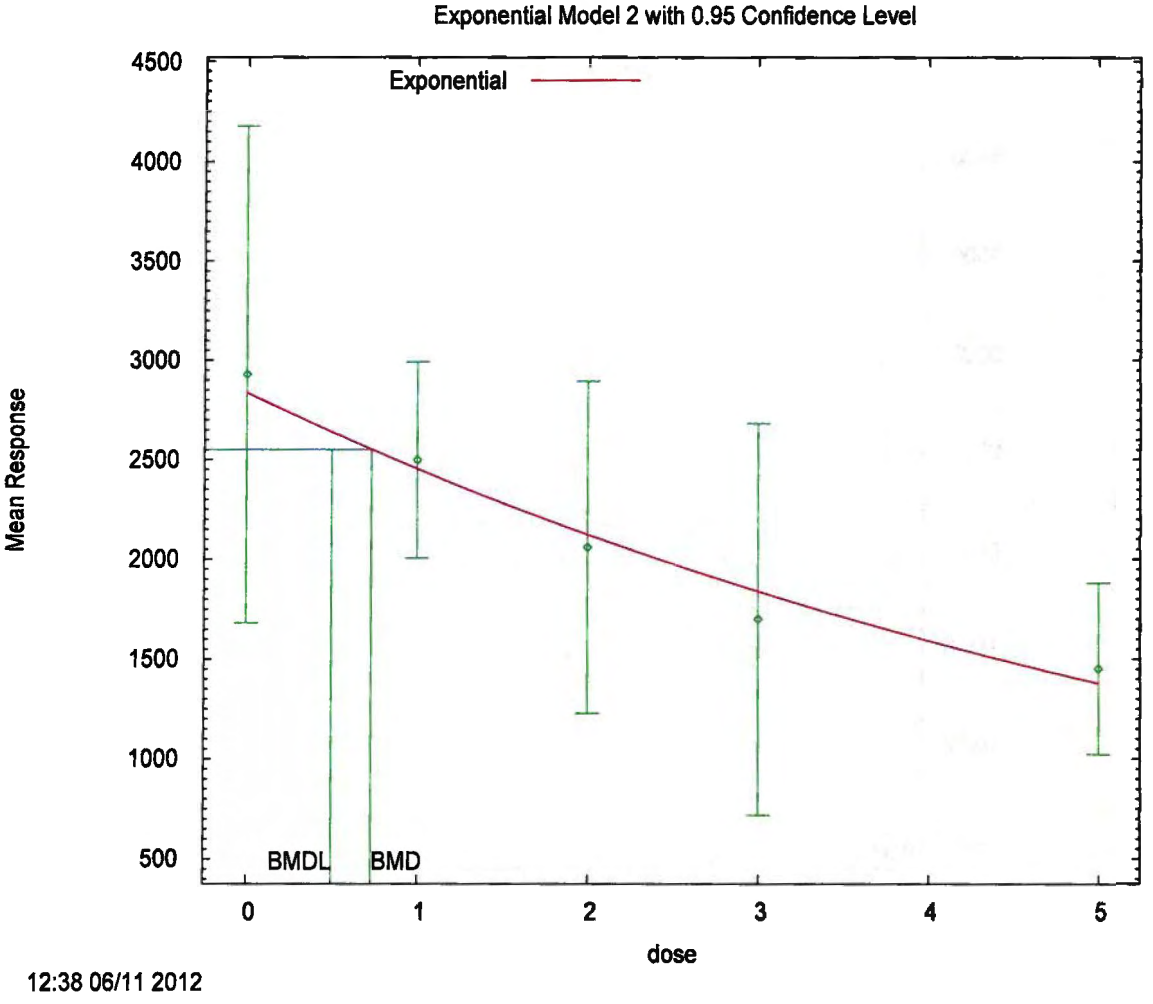
Risk Type = Relative deviation

Confidence Level = 0.950000

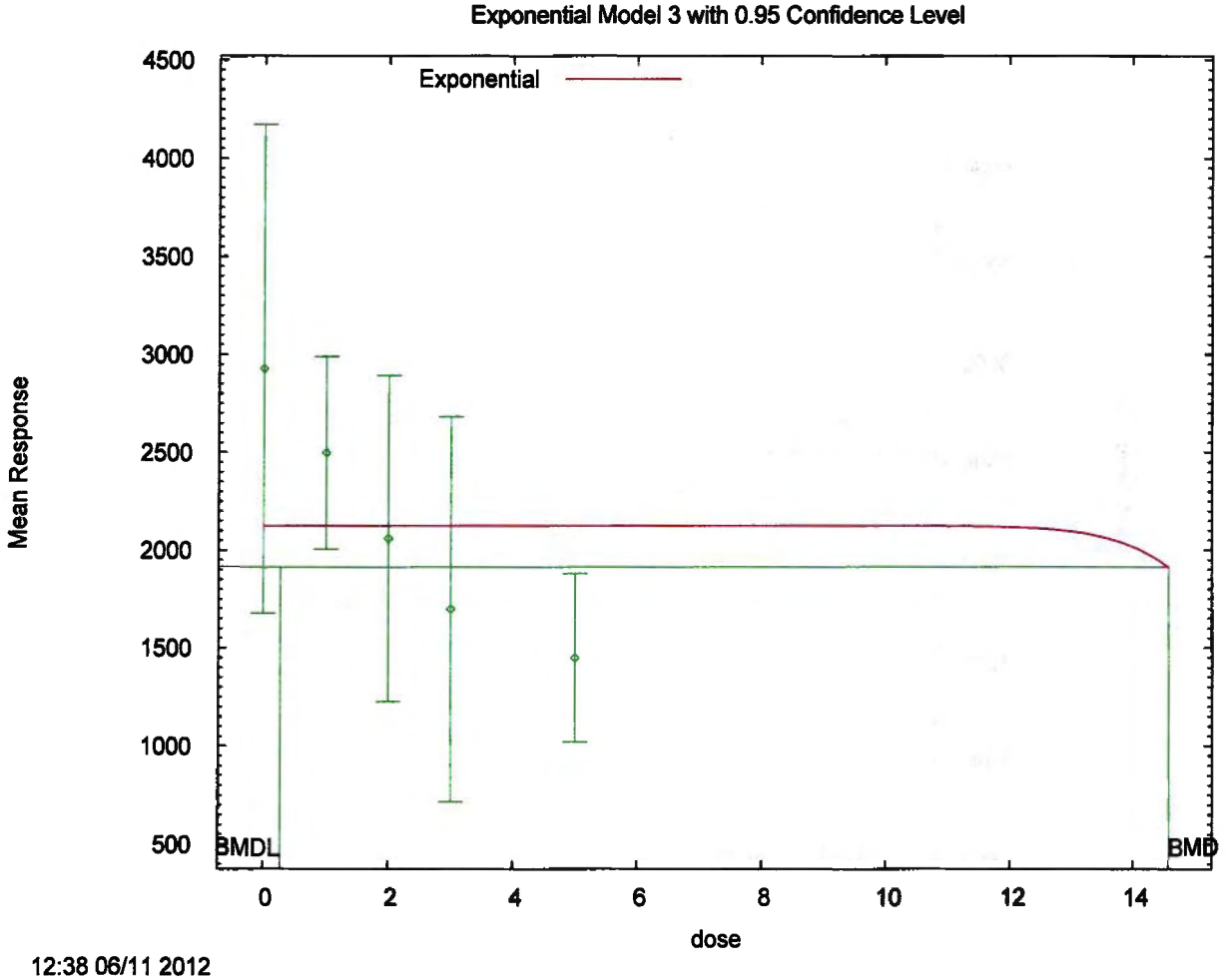
BMD and BMDL by Model

Model	BMD	BMDL
2	0.730995	0.498177
3	14.5585	0.274785
4	0.591215	0.22635
5	0.591215	0.22635

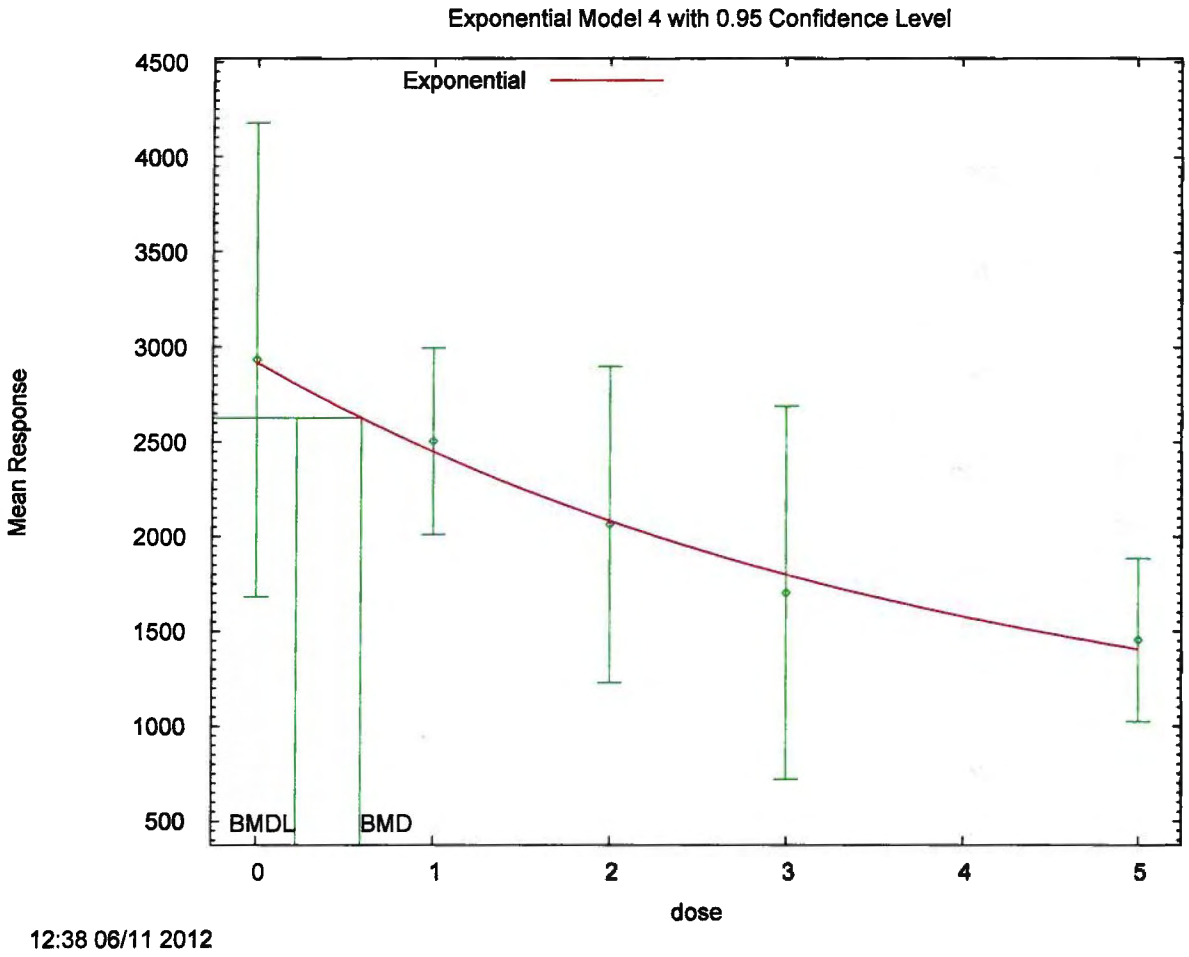
75


Exponential Model 2 with 0.95 Confidence Level
Exponential
Mean Response
4500
4000
3500
3000
2500
2000
1500
1000
500
BMDL
BMD
0
1
2
3
4
5
dose
12:38 06/11 2012

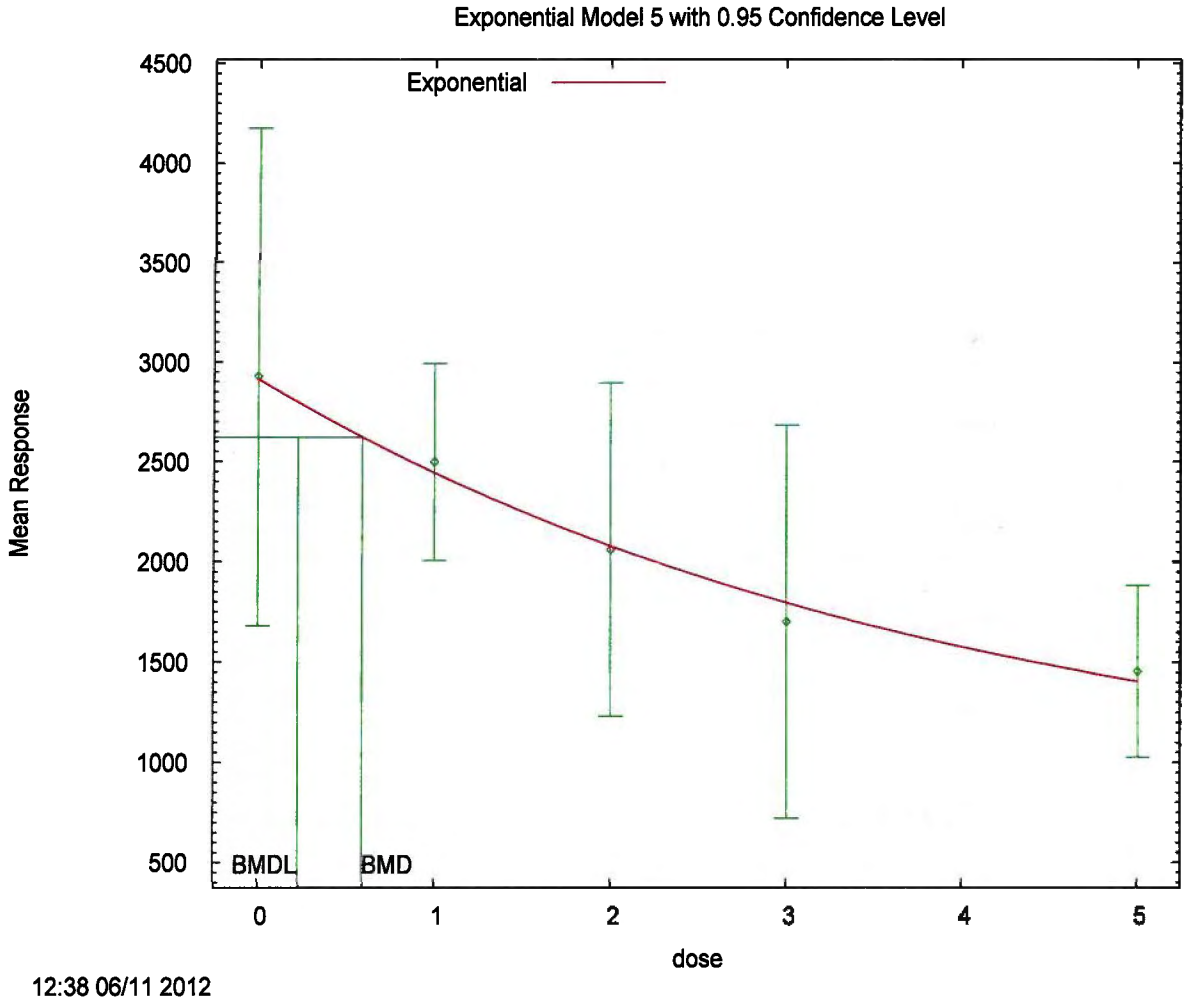
76


Exponential Model 3 with 0.95 Confidence Level
Exponential
Mean Response
4500
4000
3500
3000
2500
2000
1500
1000
500
BMDL
BMD
0
2
4
6
8
10
12
14
dose
12:38 06/11 2012

77


Exponential Model 4 with 0.95 Confidence Level
Exponential
Mean Response
4500
4000
3500
3000
2500
2000
1500
1000
500
BMDL
BMD
0
1
2
3
4
5
dose
12:38 06/11 2012

78


Exponential Model 5 with 0.95 Confidence Level
Exponential
Mean Response
4500
4000
3500
3000
2500
2000
1500
1000
500
BMDL
BMD
0
1
2
3
4
5
dose
12:38 06/11 2012

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PROPOXUR - Adult Male Brain - high dose dropped (10 mg/kg/day) [to improve fit and convergence]

BMDS 2.1.2 - Exponential Model (homogeneous variance – best fit)

BMR = 10%

Dataset: acute male adult brain at 0.25 hrs postdosing

Dose	ChE		sd	N
0	52184	U/L	1887.5	6
1	50600	U/L	2619.9	6
2	43686	U/L	2300.2	6
3	41315	U/L	3712.8	6
5	34964	U/L	4661.7	6

```
=============================================================================
        Exponential Model. (Version: 1.7;  Date: 12/10/2009)
        Input Data File: C:/Usepa/BMDS212/Data/exp_Testrunscontinuous_Setting.(d)
        Gnuplot Plotting File:
                                                  Mon Jun 11 13:01:24 2012
=============================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   rho is set to 0.
   A constant variance model is fit.

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   MLE solution provided: Exact

                              Initial Parameter Values
```

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Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	15.96	15.96	15.96	15.96
rho(S)	0	0	0	0
a	36693.2	36693.2	54793.2	54793.2
b	0.0834852	0.0834852	0.152853	0.152853
c	--	--	0.319054	0.319054
d	--	1	--	1

(S) = Specified

Parameter Estimates by Model

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	16.0798	16.072	16.0798	16.033
rho	0	0	0	0
a	52979	52657.9	52979	52488.6
b	0.0833343	0.0897811	0.0833343	0.322679
c	--	--	0	0.627572
d	--	1.08599	--	1.64519

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	6	5.218e+004	1888
1	6	5.06e+004	2620
2	6	4.369e+004	2300
3	6	4.132e+004	3713
5	6	3.496e+004	4661

Estimated Values of Interest

Model	Dose	Est Mean	Est Std	Scaled Residual
2	0	5.298e+004	3102	-0.6277
	1	4.874e+004	3102	1.466
	2	4.485e+004	3102	-0.9157
	3	4.126e+004	3102	0.04346
	5	3.493e+004	3102	0.03021
3	0	5.266e+004	3090	-0.3757
	1	4.895e+004	3090	1.306
	2	4.51e+004	3090	-1.122
	3	4.14e+004	3090	-0.06482
	5	3.463e+004	3090	0.2629
4	0	5.298e+004	3102	-0.6277
	1	4.874e+004	3102	1.466
	2	4.485e+004	3102	-0.9157
	3	4.126e+004	3102	0.04346
	5	3.493e+004	3102	0.03021
5	0	5.249e+004	3031	-0.2462
	1	4.967e+004	3031	0.7494
	2	4.496e+004	3031	-1.028
	3	4.052e+004	3031	0.6459
	5	3.511e+004	3031	-0.1209

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Other models for which likelihoods are calculated:

Model A1: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma^2$

Model A2: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma(i)^2$

Model A3: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = exp(lalpha + log(mean(i)) * rho)$

Model R: $Yij = Mu + e(i)$
$Var\{e(ij)\} = Sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-254.4003	6	520.8007
A2	-251.1922	10	522.3845
A3	-254.4003	6	520.8007
R	-280.3427	2	564.6853
2	-256.1963	3	518.3926
3	-256.0803	4	520.1606
4	-256.1963	3	518.3926
5	-255.4949	5	520.9898

Additive constant for all log-likelihoods = -27.57. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test 5a: Does Model 3 fit the data? (A3 vs. 3)
Test 5b: Is Model 3 better than Model 2? (3 vs. 2)

Test 6a: Does Model 4 fit the data? (A3 vs. 4)
Test 6b: Is Model 4 better than Model 2? (4 vs. 2)

Test 7a: Does Model 5 fit the data? (A3 vs. 5)
Test 7b: Is Model 5 better than Model 3? (5 vs. 3)
Test 7c: Is Model 5 better than Model 4? (5 vs. 4)

Tests of Interest

Test	2*log(Likelihood Ratio)	D. F.	p-value
Test 1	58.3	8	< 0.0001
Test 2	6.416	4	0.1701
Test 3	6.416	4	0.1701
Test 4	3.592	3	0.309
Test 5a	3.36	2	0.1864

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Test 5b	0.232	1	0.63
Test 6a	3.592	3	0.309
Test 6b	0	0	N/A
Test 7a	2.189	1	0.139
Test 7b	1.171	1	0.2792
Test 7c	1.403	2	0.4959

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

The p-value for Test 5a is greater than .1. Model 3 seems to adequately describe the data.

The p-value for Test 5b is greater than .05. Model 3 does not seem to fit the data better than Model 2.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Degrees of freedom for Test 6b are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 7a is greater than .1. Model 5 seems to adequately describe the data.

The p-value for Test 7b is greater than .05. Model 5 does not seem to fit the data better than Model 3.

The p-value for Test 7c is greater than .05. Model 5 does not seem to fit the data better than Model 4.

Benchmark Dose Computations:

Specified Effect = 0.100000

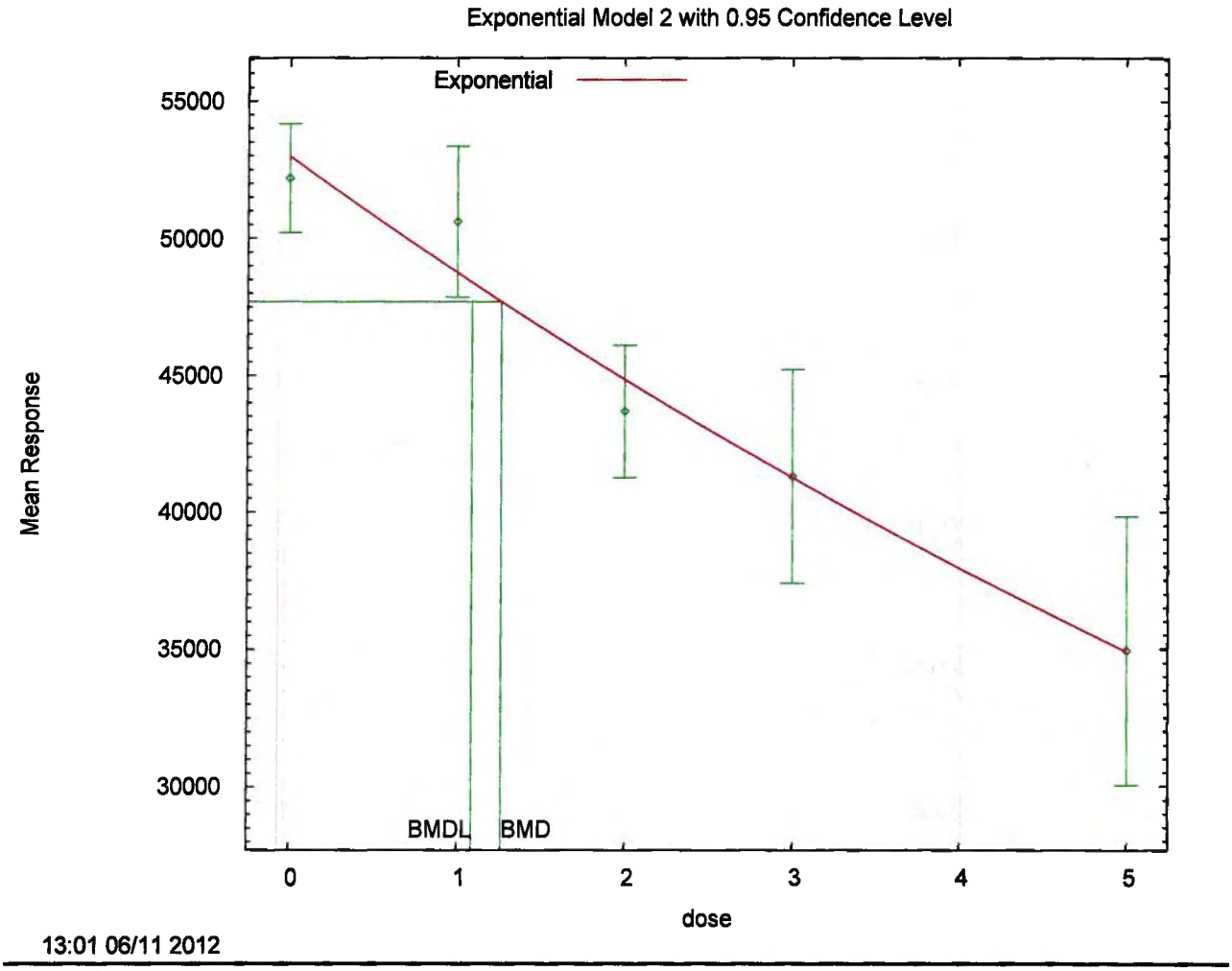
Risk Type = Relative deviation

Confidence Level = 0.950000

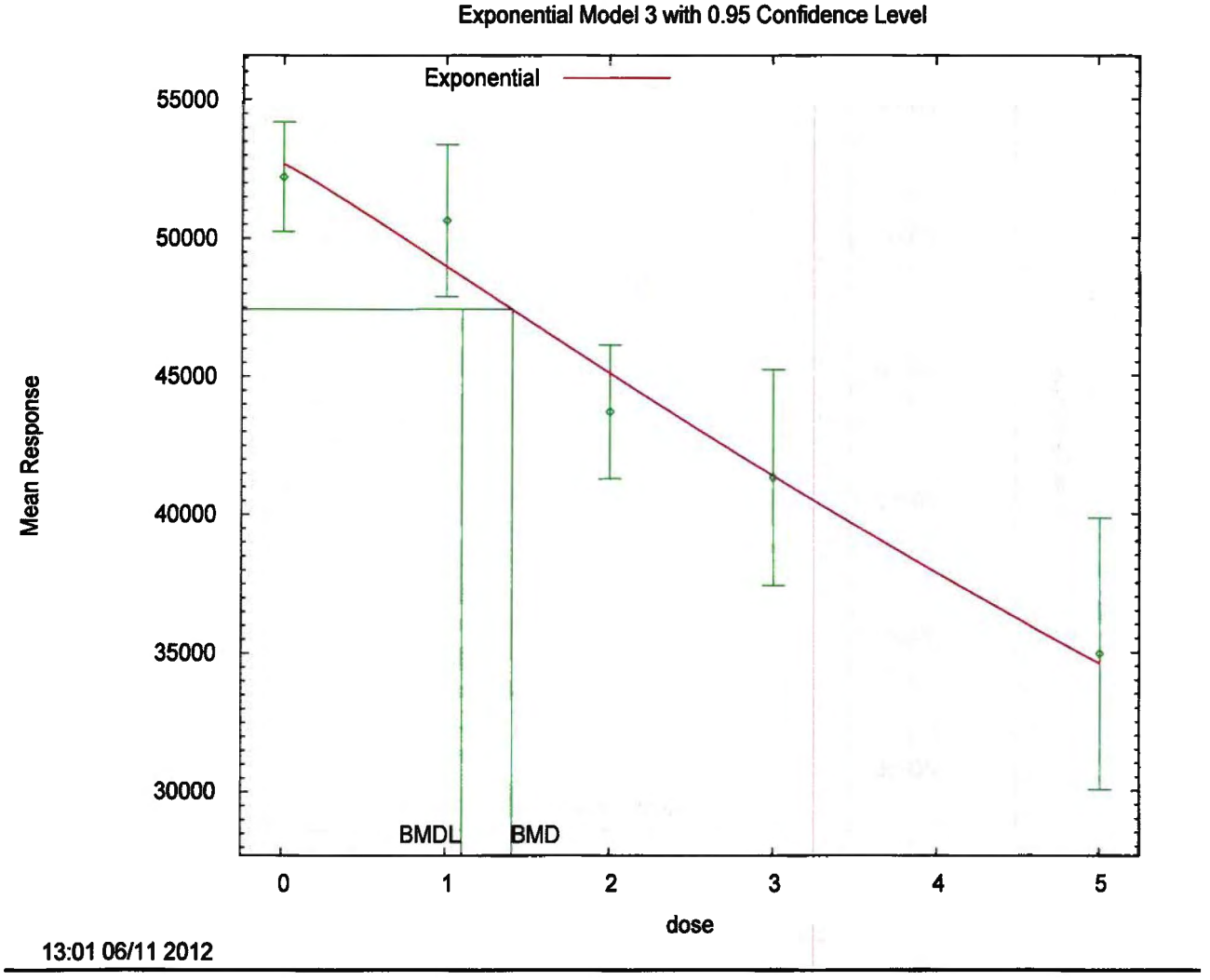
BMD and BMDL by Model

Model	BMD	BMDL
2	1.26431	1.08907
3	1.40241	1.09607
4	1.26431	0.929458
5	1.52871	1.02944

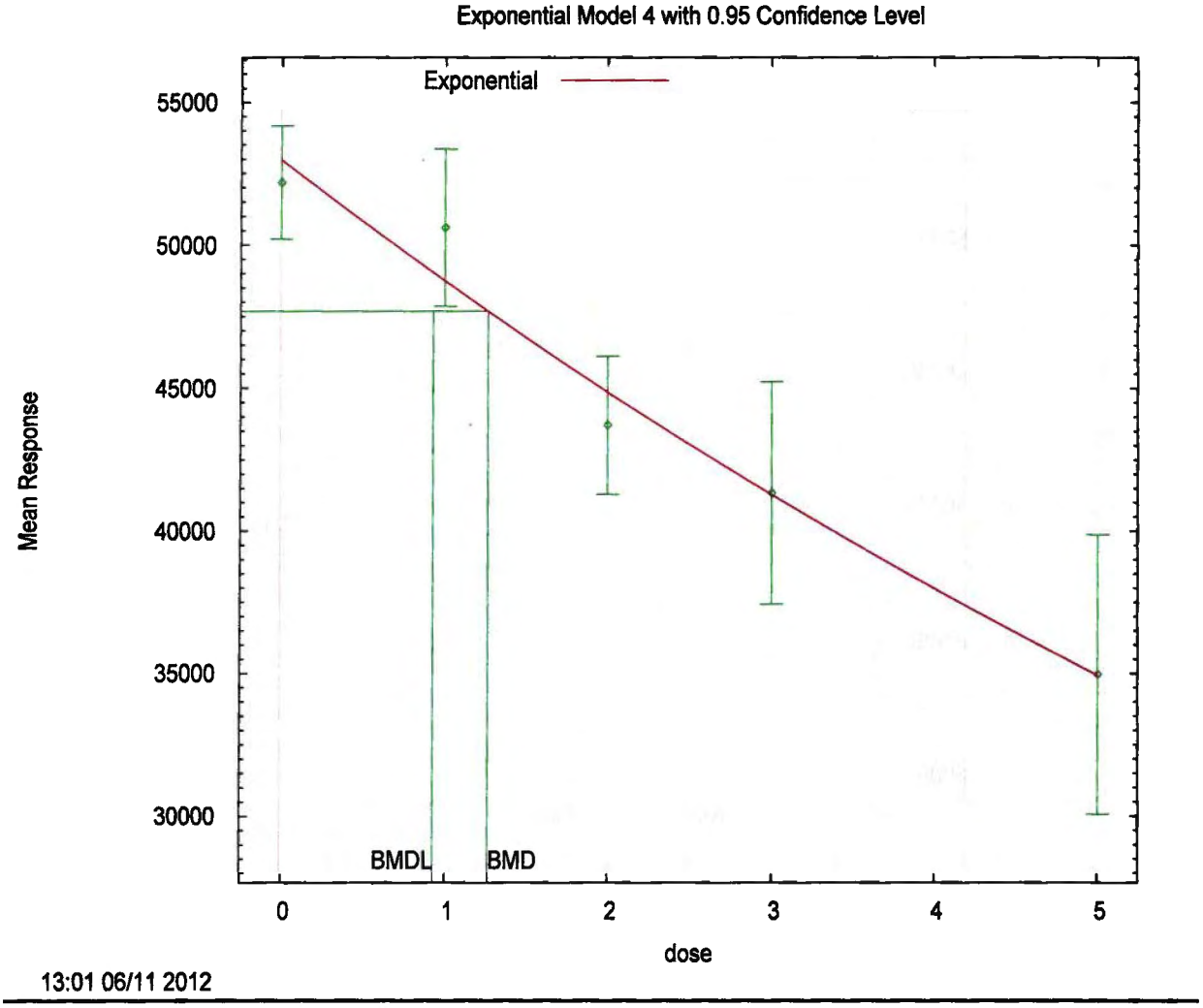
83


Exponential Model 2 with 0.95 Confidence Level
Exponential
55000
50000
45000
40000
35000
30000
Mean Response
BMDL
BMD
0
1
2
3
4
5
dose
13:01 06/11 2012

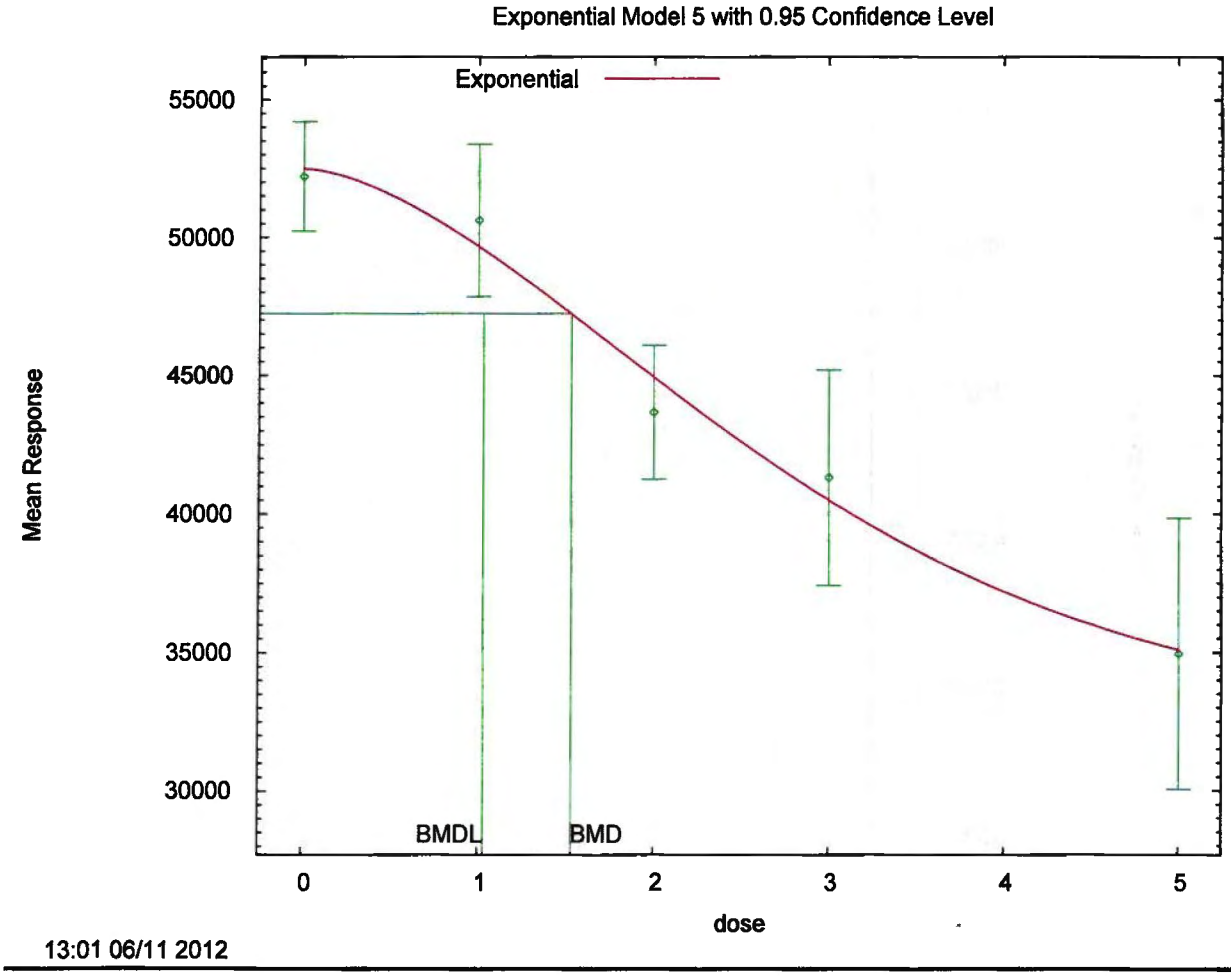
84


Exponential Model 3 with 0.95 Confidence Level
Exponential
55000
50000
45000
40000
35000
30000
Mean Response
BMDL
BMD
0
1
2
3
4
5
dose
13:01 06/11 2012

85


Exponential Model 4 with 0.95 Confidence Level
Exponential
55000
50000
45000
40000
35000
30000
Mean Response
BMDL
BMD
0
1
2
3
4
5
dose
13:01 06/11 2012

86



Selected BMDS output for Likelihood Ratio Test :

Exponential model (heterogeneous variance) Female PND11 RBC :

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-281.4468	5	572.8935
A2	-273.2373	8	562.4745
A3	-278.2065	6	568.4131
R	-301.4351	2	606.8702
2	-284.6608	4	577.3215
3	-284.6608	4	577.3215
4	-278.8974	5	567.7947
5	-278.8974	5	567.7947

Additive constant for all log-likelihoods = -34. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

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Exponential Model (heterogeneous variance) Male PND11 RBC :

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-258.8745	5	527.7491
A2	-256.3494	8	528.6987
A3	-257.6339	6	527.2678
R	-281.9828	2	567.9655
2	-257.8321	4	523.6641
3	-499.1267	4	1006.253
4	-257.6347	5	525.2694
5	-257.6347	5	525.2694

Additive constant for all log-likelihoods = -32.16. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Exponential Model (heterogeneous variance) combined PND11 RBC :

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-544.8439	5	1099.688
A2	-539.0674	8	1094.135
A3	-541.3211	6	1094.642
R	-584.2958	2	1172.592
2	-545.789	4	1099.578
3	-890.5382	4	1789.076
4	-541.693	5	1093.386
5	-541.693	5	1093.386

Additive constant for all log-likelihoods = -66.16. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

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Combined Male and Female PND11 RBC ChE Data for Dose- Response Study

```
================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\USEPA\BMDS21\hilDax_Setting.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\hilDax_Setting.plt
                                          Tue Aug 14 11:07:55 2012
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = mean
   Independent variable = dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                        lalpha =      14.1917
                           rho =            0
                     intercept =      6865.67
                             v =     -4466.78
                             n =      8.77777
                             k =     0.211717


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -n
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                  lalpha          rho    intercept            v            k

    lalpha             1           -1         0.14        -0.13       -0.056

       rho            -1            1        -0.15         0.13        0.056

 intercept          0.14        -0.15            1         -0.2        -0.61

         v         -0.13         0.13         -0.2            1        -0.59

         k        -0.056        0.056        -0.61        -0.59            1
```

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Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	4.19024	3.76642	-3.19182	11.5723
rho	1.17634	0.449021	0.296275	2.05641
intercept	6839.55	330.275	6192.22	7486.87
v	-5892.8	572.828	-7015.53	-4770.08
n	1	NA		
k	0.325016	0.115836	0.0979805	0.552051

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	18	6.87e+003	6.84e+003	1.61e+003	1.46e+003	0.0757
0.1	17	5.42e+003	5.45e+003	943	1.28e+003	-0.116
0.3	19	4.01e+003	4.01e+003	1.31e+003	1.07e+003	0.00464
1	18	2.4e+003	2.39e+003	760	789	0.036

Model Descriptions for likelihoods calculated

Model A1: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma^2$

Model A2: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma(i)^2$

Model A3: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = exp(lalpha + rho*ln(Mu(i)))$
Model A3 uses any fixed variance parameters that were specified by the user

Model R: $Yi = Mu + e(i)$
$Var\{e(i)\} = Sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-544.843935	5	1099.687870
A2	-539.067392	8	1094.134785
A3	-541.321057	6	1094.642113
fitted	-541.453167	5	1092.906334
R	-584.295799	2	1172.591599

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Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	90.4568	6	<.0001
Test 2	11.5531	3	0.009082
Test 3	4.50733	2	0.105
Test 4	0.264221	1	0.6072

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Relative risk

Confidence level = 0.95

BMD = 0.0426766

BMDL = 0.0285396

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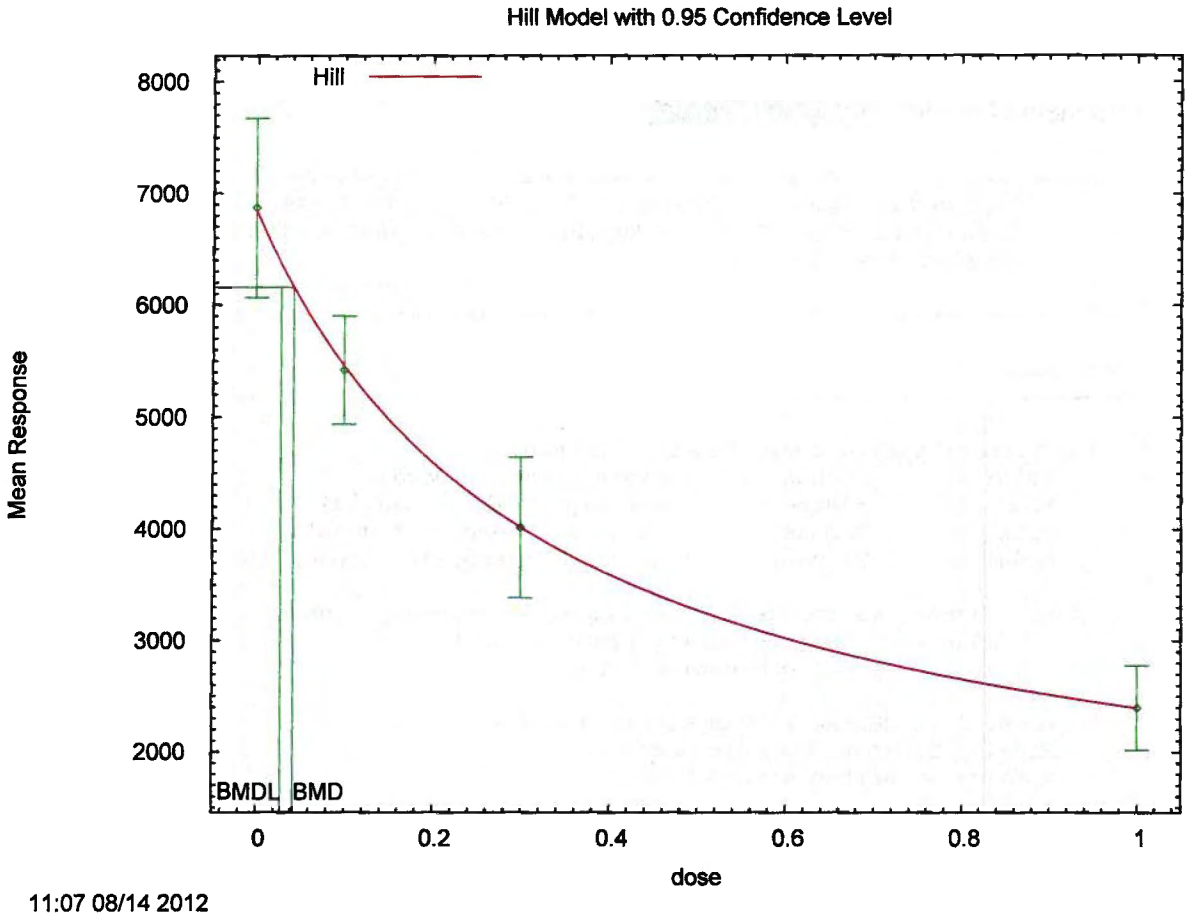
Hill Model with 0.95 Confidence Level
Hill
8000
7000
6000
5000
4000
3000
2000
Mean Response
BMDL
BMD
0
0.2
0.4
0.6
0.8
1
dose
11:07 08/14 2012

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Propoxur CCA Dose range study – combined sexes: adult male and female RBC combined

EPA BMDS v2.12
Exponential model – nonhomogeneous

```
 ================================================================
        Exponential Model. (Version: 1.7;  Date: 12/10/2009)
        Input Data File: C:/Usepa/BMDS212/Data/exp_UntitledData_Setting.(d)
        Gnuplot Plotting File:
                                              Thu Aug 16 11:12:56 2012
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   MLE solution provided: Exact

                              Initial Parameter Values

     Variable          Model 2          Model 3          Model 4          Model 5
     --------          -------          -------          -------          -------
     lnalpha           7.48339          7.48339          7.48339          7.48339
         rho          0.731572         0.731572         0.731572         0.731572
           a           1106.16          1106.16           3227.7           3227.7
           b          0.132095         0.132095         0.385352         0.385352
           c                --               --         0.236888
0.236888
           d                --                1               --                1

                            Parameter Estimates by Model
```

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	8.49327	8.49326	6.8027	6.80955
rho	0.605466	0.605468	0.823266	0.82231
a	2929.5	2929.5	3134.12	3119.12
b	0.149886	0.149886	0.291311	0.298776
c	--	--	0.224916	0.237499
d	--	1	--	1.05216

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	12	3074	1014
1	12	2598	593.1
2	12	2110	684.4
3	12	1608	772.2
5	12	1350	413.1
10	12	802.8	565.8

Estimated Values of Interest

Model	Dose	Est Mean	Est Std	Scaled Residual
2	0	2929	783.1	0.6392
	1	2522	748.3	0.3538
	2	2171	715.1	-0.2965
	3	1869	683.4	-1.322
	5	1385	624.1	-0.1938
	10	654.4	497.4	1.034
3	0	2929	783.1	0.6392
	1	2522	748.3	0.3538
	2	2171	715.1	-0.2965
	3	1869	683.4	-1.322
	5	1385	624.1	-0.1938
	10	654.4	497.4	1.034
4	0	3134	824.7	-0.2525
	1	2520	753.9	0.3582
	2	2061	694.1	0.2398
	3	1719	644	-0.596
	5	1271	568.8	0.479
	10	836.8	478.9	-0.2459
5	0	3119	822.7	-0.19
	1	2537	755.8	0.2788
	2	2070	695.1	0.1962
	3	1716	643.6	-0.5837
	5	1258	566.4	0.5599
	10	841.4	480.1	-0.278

Other models for which likelihoods are calculated:

Model A1: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma^2$

Model A2: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma(i)^2$

Model A3: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = exp(lalpha + log(mean(i)) * rho)$

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Model R: Yij = Mu + e(i)
Var{e(ij)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-504.4921	7	1022.984
A2	-499.0298	12	1022.06
A3	-502.2509	8	1020.502
R	-534.4764	2	1072.953
2	-504.3179	4	1016.636
3	-504.3179	4	1016.636
4	-502.3881	5	1014.776
5	-502.3774	6	1016.755

Additive constant for all log-likelihoods = -66.16. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test 5a: Does Model 3 fit the data? (A3 vs 3)
Test 5b: Is Model 3 better than Model 2? (3 vs. 2)

Test 6a: Does Model 4 fit the data? (A3 vs 4)
Test 6b: Is Model 4 better than Model 2? (4 vs. 2)

Test 7a: Does Model 5 fit the data? (A3 vs 5)
Test 7b: Is Model 5 better than Model 3? (5 vs. 3)
Test 7c: Is Model 5 better than Model 4? (5 vs. 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	70.89	10	< 0.0001
Test 2	10.92	5	0.0529
Test 3	6.442	4	0.1685
Test 4	4.134	4	0.3882
Test 5a	4.134	4	0.3882
Test 5b	-9.3e-011	0	N/A
Test 6a	0.2744	3	0.9648
Test 6b	3.86	1	0.04946
Test 7a	0.2531	2	0.8811
Test 7b	3.881	2	0.1436
Test 7c	0.02129	1	0.884

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

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The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

The p-value for Test 5a is greater than .1. Model 3 seems to adequately describe the data.

Degrees of freedom for Test 5b are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

The p-value for Test 6b is less than .05. Model 4 appears to fit the data better than Model 2.

The p-value for Test 7a is greater than .1. Model 5 seems to adequately describe the data.

The p-value for Test 7b is greater than .05. Model 5 does not seem to fit the data better than Model 3.

The p-value for Test 7c is greater than .05. Model 5 does not seem to fit the data better than Model 4.

Benchmark Dose Computations:

Specified Effect = 0.100000

Risk Type = Relative deviation

Confidence Level = 0.950000

BMD and BMDL by Model

Model	BMD	BMDL
2	0.702937	0.557075
3	0.702937	0.557075
4	0.474181	0.339178
5	0.51859	0.339621

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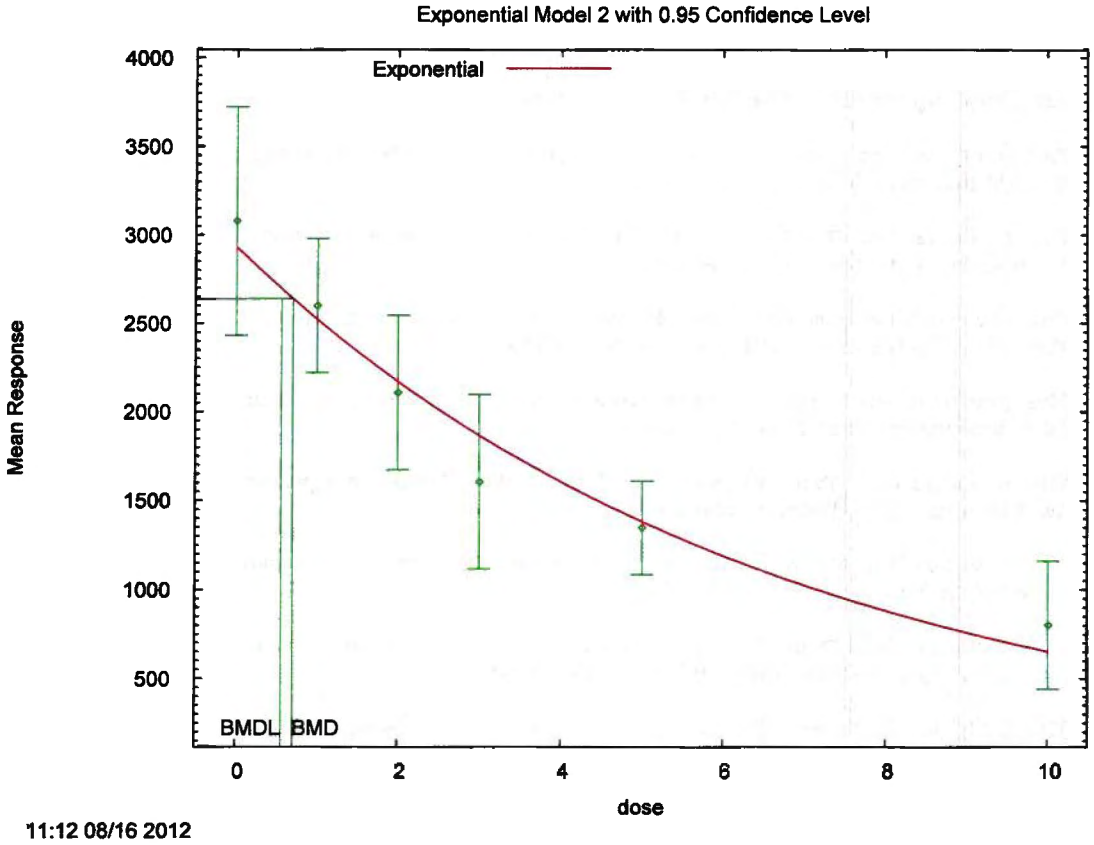
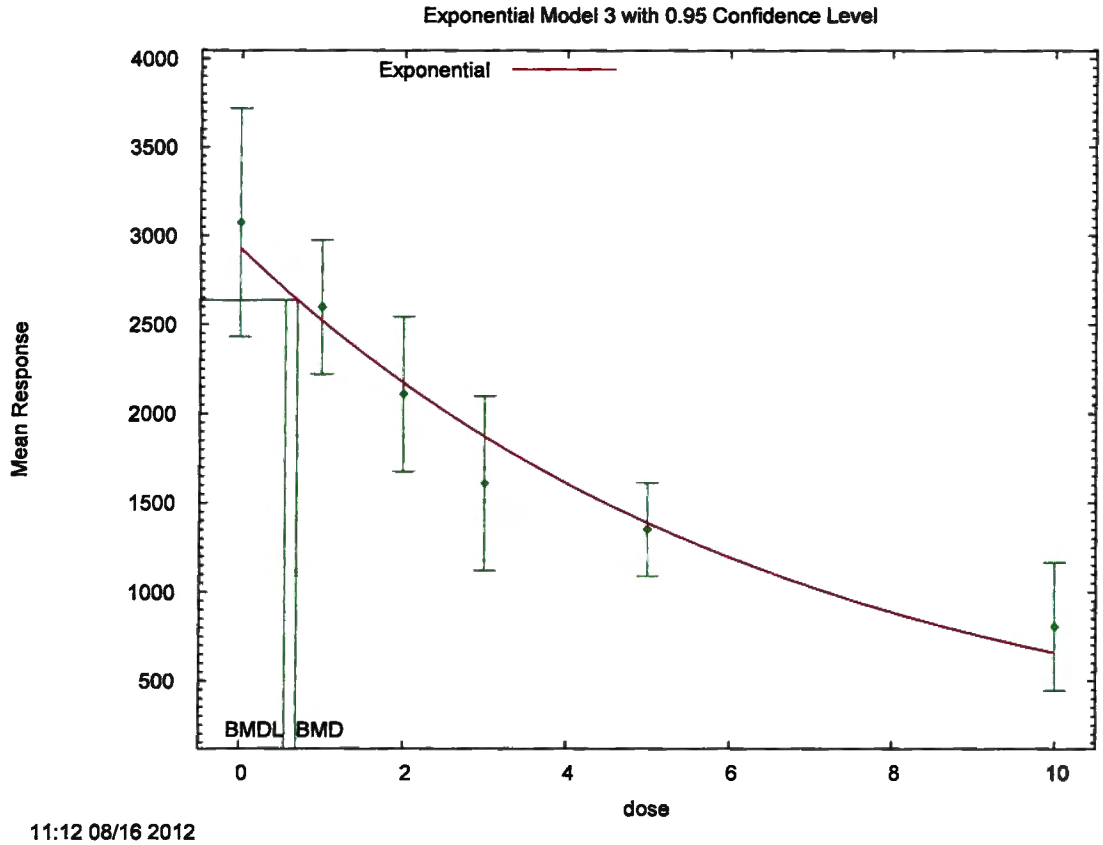

Exponential Model 2 with 0.95 Confidence Level
Exponential
Mean Response
4000
3500
3000
2500
2000
1500
1000
500
BMDL
BMD
0
2
4
6
8
10
dose
11:12 08/16 2012

97


Exponential Model 3 with 0.95 Confidence Level
Exponential
Mean Response
dose
BMDL
BMD
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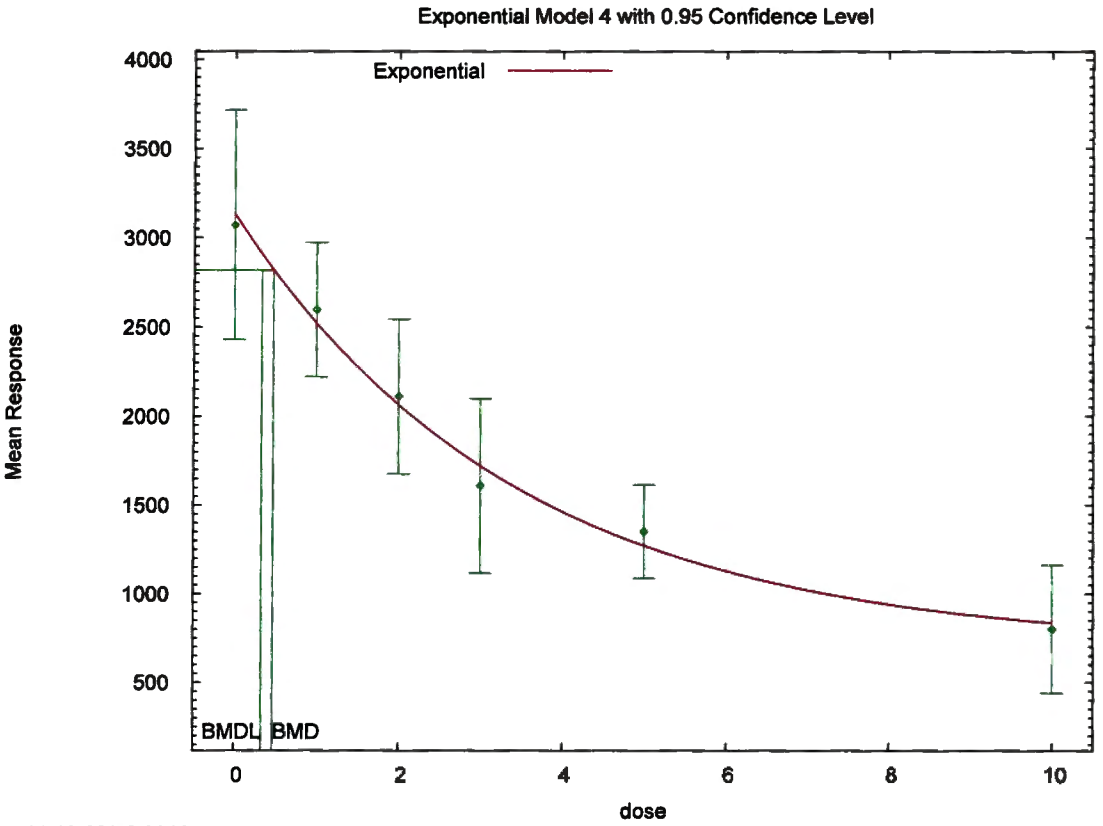
3500
3000
2500
2000
1500
1000
500
0
2
4
6
8
10
11:12 08/16 2012


Exponential Model 4 with 0.95 Confidence Level
Exponential
Mean Response
dose
BMDL
BMD
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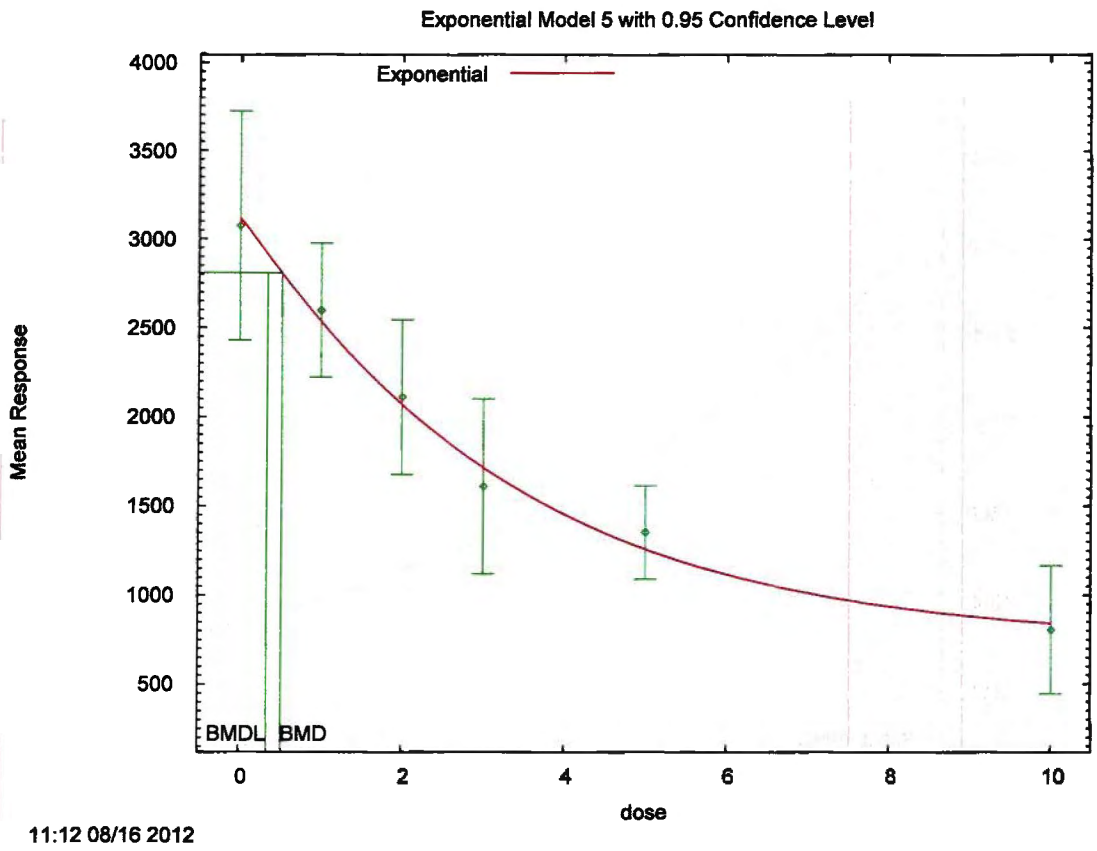
3500
3000
2500
2000
1500
1000
500
0
2
4
6
8
10
11:12 08/16 2012

98


Exponential Model 5 with 0.95 Confidence Level
Exponential
Mean Response
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3500
3000
2500
2000
1500
1000
500
BMDL
BMD
0
2
4
6
8
10
dose
11:12 08/16 2012

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Propoxur CCA Dose-Range study – combined sexes adult male and female brain

EPA BMDS v2.12
Exponential model – nonhomogeneous

```
 ================================================================
        Exponential Model. (Version: 1.7;  Date: 12/10/2009)
        Input Data File: C:/Usepa/BMDS212/Data/exp_UntitledData_Setting.(d)
        Gnuplot Plotting File:
                                              Thu Aug 16 12:06:49 2012
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   MLE solution provided: Exact

                              Initial Parameter Values

     Variable          Model 2          Model 3          Model 4          Model 5
     --------          -------          -------          -------          -------
     lnalpha           67.4078          67.4078          67.4078          67.4078
         rho          -4.79547         -4.79547         -4.79547         -4.79547
           a             30110            30110            54464.4          54464.4
           b         0.0704899        0.0704899         0.313747         0.313747
           c                --               --         0.458415
0.458415
           d                --                1               --                1


                              Parameter Estimates by Model

     Variable          Model 2          Model 3          Model 4          Model 5
```


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lnalpha	54.5481	54.5481	63.3663	65.4174
rho	-3.58247	-3.58247	-4.40747	-4.60927
a	52289.6	52289.6	52499.6	51994.5
b	0.0990209	0.0990209	0.176593	0.284735
c	--	--	0.359934	0.501383
d	--	1	--	1.49384

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	12	5.187e+004	1588
1	12	4.854e+004	3268
2	12	4.291e+004	3881
3	12	3.776e+004	4438
5	12	3.062e+004	7247
10	12	2.622e+004	1.094e+004

Estimated Values of Interest

Model	Dose	Est Mean	Est Std	Scaled Residual
2	0	5.229e+004	2473	-0.5866
	1	4.736e+004	2953	1.385
	2	4.289e+004	3526	0.01581
	3	3.885e+004	4210	-0.9012
	5	3.187e+004	6003	-0.7219
	10	1.943e+004	1.457e+004	1.614
3	0	5.229e+004	2473	-0.5866
	1	4.736e+004	2953	1.385
	2	4.289e+004	3526	0.01581
	3	3.885e+004	4210	-0.9012
	5	3.187e+004	6003	-0.7219
	10	1.943e+004	1.457e+004	1.614
4	0	5.25e+004	2280	-0.9555
	1	4.706e+004	2901	1.768
	2	4.25e+004	3631	0.3913
	3	3.868e+004	4469	-0.7163
	5	3.279e+004	6430	-1.171
	10	2.464e+004	1.207e+004	0.4512
5	0	5.199e+004	2171	-0.1973
	1	4.831e+004	2571	0.3049
	2	4.291e+004	3379	-0.002005
	3	3.783e+004	4518	-0.05872
	5	3.083e+004	7241	-0.1
	10	2.629e+004	1.045e+004	-0.02404

Other models for which likelihoods are calculated:

Model A1: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma^2$

Model A2: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma(i)^2$

Model A3: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = \exp(lalpha + \log(mean(i)) * rho)$

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Model R: Yij = Mu + e(i)
Var{e(ij)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-659.9218	7	1333.844
A2	-636.6195	12	1297.239
A3	-638.6038	8	1293.208
R	-705.0244	2	1414.049
2	-643.2422	4	1294.484
3	-643.2422	4	1294.484
4	-641.6889	5	1293.378
5	-638.6195	6	1289.239

Additive constant for all log-likelihoods = -66.16. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test 5a: Does Model 3 fit the data? (A3 vs 3)
Test 5b: Is Model 3 better than Model 2? (3 vs. 2)

Test 6a: Does Model 4 fit the data? (A3 vs 4)
Test 6b: Is Model 4 better than Model 2? (4 vs. 2)

Test 7a: Does Model 5 fit the data? (A3 vs 5)
Test 7b: Is Model 5 better than Model 3? (5 vs. 3)
Test 7c: Is Model 5 better than Model 4? (5 vs. 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	136.8	10	< 0.0001
Test 2	46.6	5	< 0.0001
Test 3	3.969	4	0.4103
Test 4	9.277	4	0.05454
Test 5a	9.277	4	0.05454
Test 5b	2.274e-013	0	N/A
Test 6a	6.17	3	0.1036
Test 6b	3.107	1	0.07798
Test 7a	0.03139	2	0.9844
Test 7b	9.245	2	0.009826
Test 7c	6.139	1	0.01322

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous

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variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 4 is less than .1. Model 2 may not adequately describe the data; you may want to consider another model.

The p-value for Test 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model.

Degrees of freedom for Test 5b are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

The p-value for Test 6b is greater than .05. Model 4 does not seem to fit the data better than Model 2.

The p-value for Test 7a is greater than .1. Model 5 seems to adequately describe the data.

The p-value for Test 7b is less than .05. Model 5 appears to fit the data better than Model 3.

The p-value for Test 7c is less than .05. Model 5 appears to fit the data better than Model 4.

Benchmark Dose Computations:

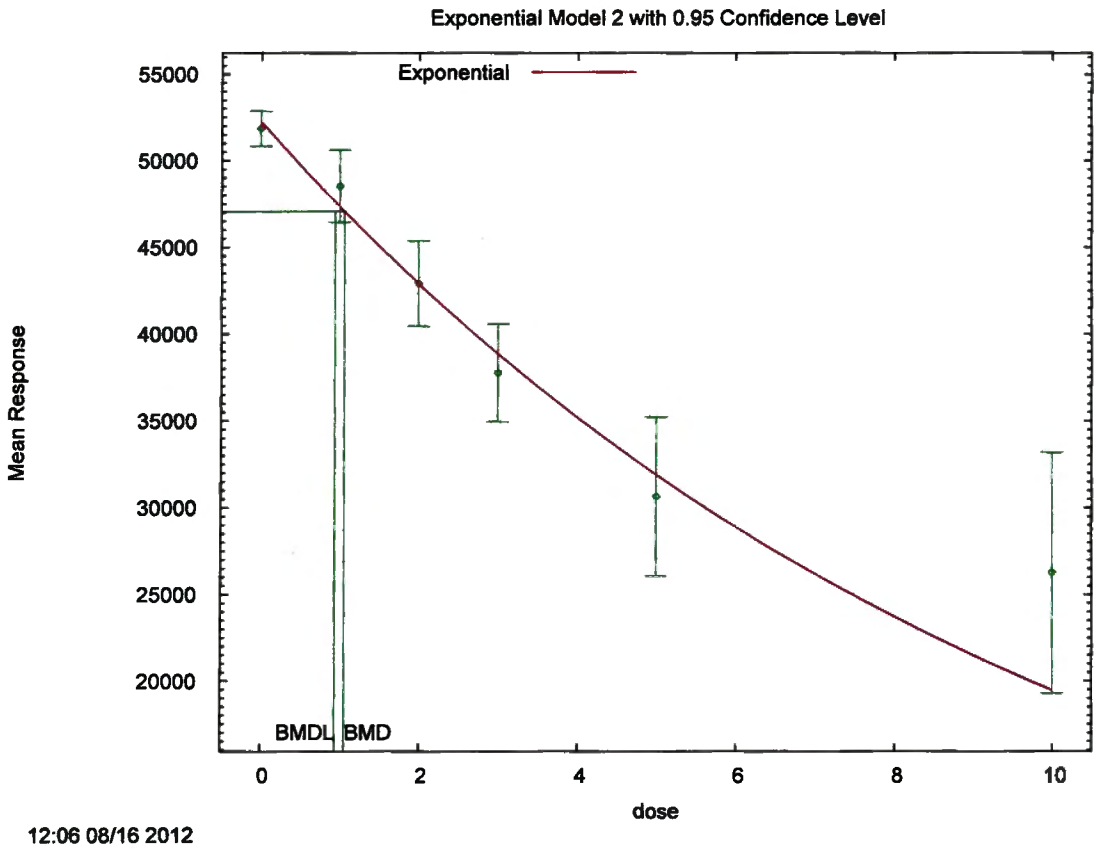
Specified Effect = 0.100000

Risk Type = Relative deviation

Confidence Level = 0.950000

BMD and BMDL by Model

Model	BMD	BMDL
2	1.06402	0.944464
3	1.06402	0.944464
4	0.961987	0.822887
5	1.28942	1.03778


Exponential Model 2 with 0.95 Confidence Level
Exponential
55000
50000
45000
40000
35000
30000
25000
20000
Mean Response
BMDL
BMD
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2
4
6
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dose
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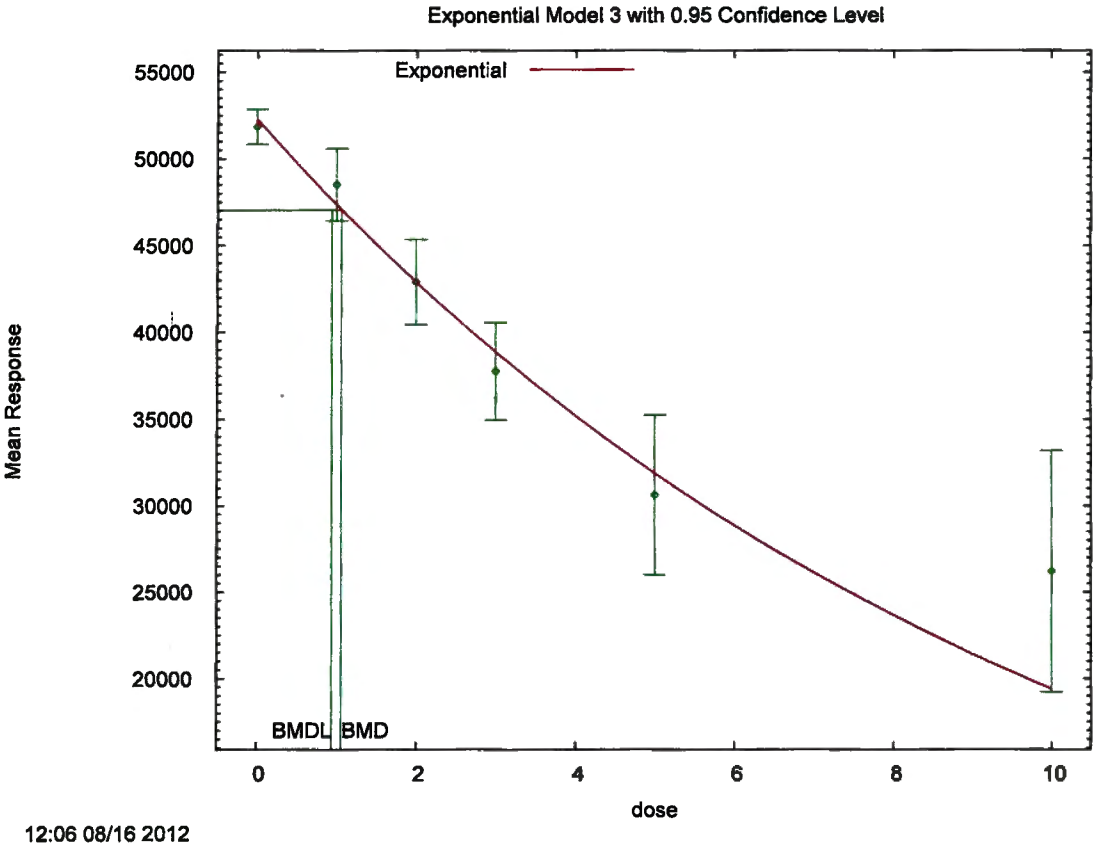
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Exponential
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Mean Response
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BMD
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2
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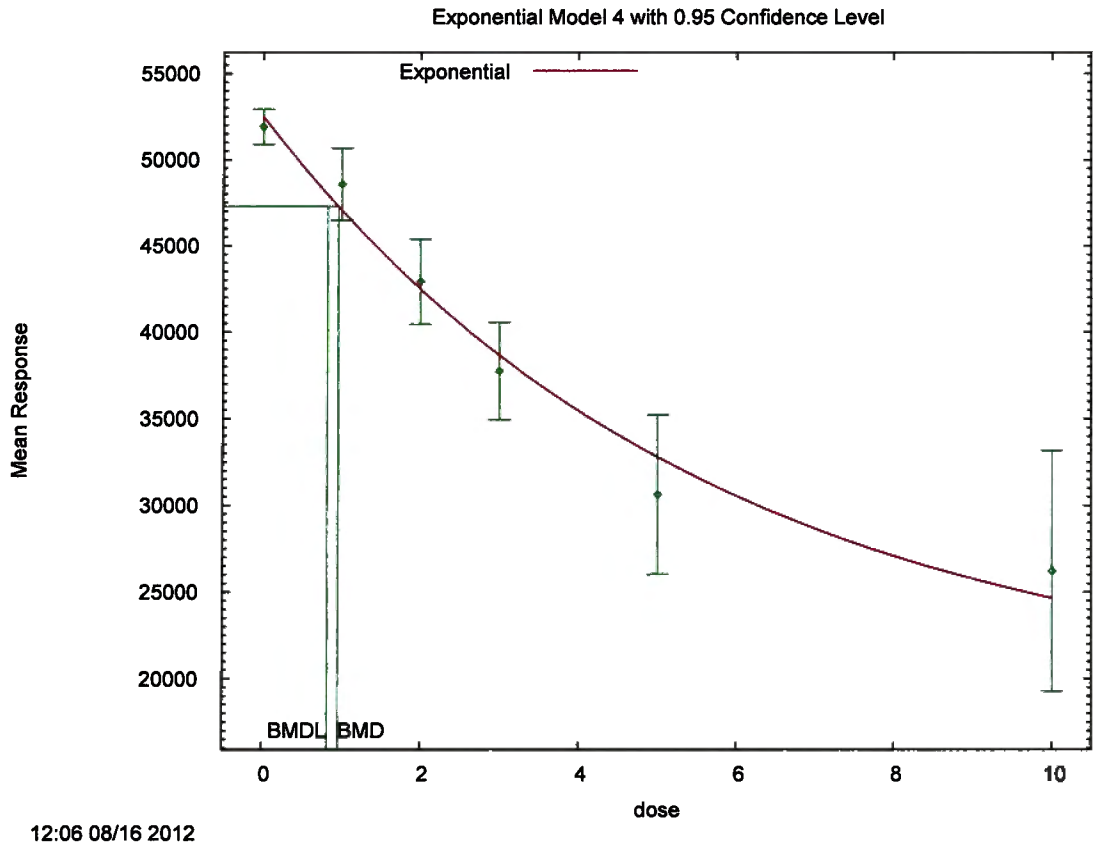
Exponential Model 4 with 0.95 Confidence Level
Exponential
Mean Response
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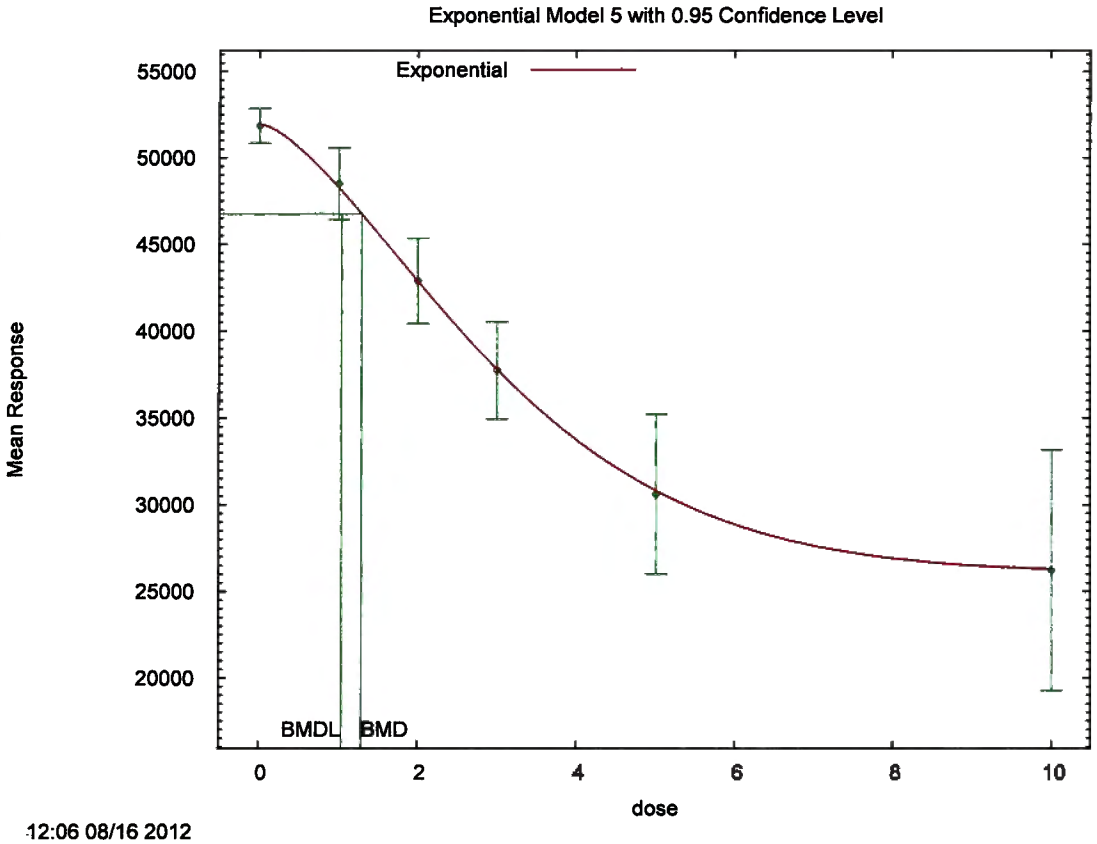
Exponential Model 5 with 0.95 Confidence Level
Exponential
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dose
12:06 08/16 2012

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